A NOVEL ANIMAL MODEL FOR PANIC DISORDER: ATTEMPTED REPRODUCTION OF THE FEAR OF FEAR

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ABSTRACT

Title of Thesis: A Novel Animal Model for Panic Disorder: Attempted Reproduction of the Fear of Fear

Jeffrey H. Cook, Master of Science, 1999

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Panic disorder is a debilitating psychiatric illness with an unknown etiology. There are numerous theories for the onset and maintenance of panic disorder, including biologically based and psychologically based models. One popular theory for panic disorder involves classical conditioning, proposing that bodily sensations of arousal elicit panic attacks. Developing a valid animal model of the classical conditioning theory of panic disorder would be a significant contribution to the literature of panic disorder. The present experiments investigated whether pharmacologically-induced sensations of arousal could function as conditioned stimuli (CS) in a conditioned suppression paradigm. Experiment 1 paired the stimulus effects of epinephrine (0.1 mg/kg, ip) with inescapable footshocks (#200, 1-mA, 0.5 sec.) using 8 male Sprague-Dawley rats. Despite repeated pairings in the paired group (n=4), epinephrine did not suppress operant responding when administered alone; indeed, rats in the control group (n=4) paradoxically demonstrated greater suppression. Experiment 2 examined the ability of yohimbine (1.0 mg/kg, ip) to serve as a CS for conditioned suppression in 8 male Sprague-Dawley rats. Despite repeated pairings, yohimbine did not suppress operant responding. Possible reasons for the lack of conditioning to the drugs are discussed.

A Novel Animal Model for Panic Disorder:
Attempted Reproduction of the Fear of Fear

by

Jeffrey H. Cook

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INTRODUCTION

Since its recognition as a discrete psychiatric syndrome in 1980, panic disorder has been the focus of intense controversy in terms of etiology, treatment, and syndromal validity (McNally, 1994). The syndrome of panic disorder is characterized by the experience of recurrent, unexpected (spontaneous) panic attacks. These attacks are usually accompanied by either anticipatory anxiety or worries regarding the possibility of having another attack (Barlow, 1988; American Psychological Association [APA], 1994). Panic attacks may lead to the development of agoraphobic avoidance, in which individuals avoid situations where they have experienced panic attacks in the past.

The American Psychological Association's Diagnostic and Statistical Manual 4th edition (DSM-IV) characterizes panic attacks as discrete episodes of intense fear which develop suddenly and may occur with (situational) or without (spontaneous) clear environmental antecedents. Panic attacks are not considered a distinct disorder, but a possible component of syndromes, because they occur across a range of anxiety and affective disorders (Barlow, 1988; APA, 1994). Panic attacks are characterized by physiological symptoms such as palpitations, trembling, sweating, dizziness, chest pain, chills/hot flashes, choking sensations, and nausea. Additionally, cognitive symptoms may be present, including depersonalization, derealization, fear of dying, and fear of losing control or going crazy. To meet DSM-IV criteria for a panic attack there must be four of the above symptoms, and they must start abruptly and peak after ten minutes (APA, 1994).

States of panic can be distinguished from anxiety states by the suddenness of onset, number and severity of symptoms and the presence of fears of dying, going crazy, or losing control (Argyle & Roth, 1989; APA, 1994). Panic typically has a very rapid onset and short duration, whereas gradual onset and chronic duration characterize anxiety states. Additionally, panic states have a greater number of symptoms, and also have more severe symptoms when compared to anxiety states (Argyle & Roth, 1989; APA, 1994). Panic and anxiety can also be differentiated in terms of their theoretical function. Panic serves a fight-or-flight function that is directed towards some immediate threat, and is thus arguably considered a state of extreme fear (Barlow, 1988). Anxiety is often defined as a state that is qualitatively different from panic. The function of anxiety is increased vigilance, which is directed towards some future (non-immediate) threat. Additionally, anxiety states lack the fight-or-flight and fear of dying/going crazy components of panic attacks (Barlow, 1988).

Various categorization schemes for panic attacks have been proposed. Attacks without an identifiable trigger are called "unexpected" (APA, 1994), "spontaneous" (Klein, 1993), and "uncued/unexpected" (Barlow, 1988). Panic attacks for which a patient can identify a triggering stimulus have been termed situationally bound or situationally predisposed (APA, 1994; Klein, 1981). Under the DSM-IV's classification system, only external stimuli can trigger panic attacks. Other classification systems are broader, allowing the inclusion of panic attacks triggered by internal stimuli (Barlow, 1988; Craske, 1991). Two additional types of panic attacks are nocturnal panic (panic occurring during sleep), and relaxation-induced panic (occurring during relaxation). A full discussion of the relative strengths and weaknesses of these classification schemes can be found elsewhere (McNally, 1994).

Although there is agreement in terms of the DSM-IV for the symptoms of this disorder; the etiology of panic disorder remains the subject of intense controversy. A review of popular theories for the etiology of panic disorder is presented in the present thesis. While there is no consensus as to which theory best accounts for panic disorder, a large body of evidence supports an interoceptive-conditioning model of panic disorder. The present thesis argues that the interoceptive-conditioning model offers the most parsimonious explanation for panic disorder. The potential utility of animal models for empirically testing etiological models of panic disorder or panic attacks is then suggested. While several animal models for panic disorder have been proposed to date, it will be argued that none have modeled specific theories for the etiology of panic disorder. Following a review and critique of these models, a novel animal model of panic disorder specifically designed to test the interoceptive conditioning theory of panic disorder is presented and empirically assessed.

ETIOLOGICAL MODELS OF PANIC DISORDER

Over the past two decades, numerous theories for the etiology of panic disorder have been advanced. Etiological theories for panic have traditionally been grouped into two domains, biological and psychological (McNally, 1994). Of these two domains, the most numerous by far are the biologically based theories, which have implicated a variety of neurotransmitter systems and neuroanatomical structures in the pathogenesis of panic disorder.

Data from biological challenge studies are intimately related to both biological and psychological models. Biological challenge studies typically involve the administration of either a drug (e. g., caffeine, yohimbine, flumazenil) or manipulations of carbon dioxide (CO_2) via inhalation of carbon dioxide or hyperventilation. These manipulations elicit intense physical sensations when administered and cause panic attacks in panic disorder patients at much higher rates than in psychiatric or healthy controls (McNally, 1994). Biological models assume that the agents administered in biological challenge procedures provoke panic attacks by exacerbating an underlying dysfunction in the neurobiological substrate affected by the agent. Indeed, many of the biological accounts were generated from experiments using biological challenge paradigms (Nutt & Lawson, 1992). Various pharmacological agents have been used to induce panic attacks, including sodium lactate (Pitts & McClure, 1967), yohimbine (Charney, Heninger, & Breier, 1984), isoproterenol (Rainy et al., 1984), carbon dioxide (van den Hout, 1988), caffeine (Charney, Heninger, and Jatlow, 1985), cholecystokinin (Bradwejn, Kosztcki, & Shriqui, 1991), and pentagastrin (Abelson & Neese, 1990). Flumazenil (Nutt, Glue, Lawson, & Wilson, 1990), $^{m-}$CPP (Kahn, Wetzler, & van Praag, 1988), epinephrine (Veltman, van Zijdarveld, & van Dyck, 1996), and β-CCE (Dorow & Horowski, 1983) have also been successfully used to induce panic attacks.

Results of studies employing biological challenges have traditionally been interpreted in accord with one of the two domains mentioned above (biological or psychological). The biological interpretation of the higher rates of panic attacks in panic disorder patients is that the challenge agent is triggering some biologically based dysfunction (either central or peripheral). The psychological interpretation is that panic disorder patients are prone to fear of the bodily sensations that challenge agents produce, and that these bodily sensations serve to trigger the panic attack (McNally, 1994).

The results of studies that have employed biological challenge agents have produced many theories implicating specific neurotransmitters system or neuroanatomical structures as dysfunctional in panic disorder. A comprehensive review of all biological theories is beyond the scope of this paper. However, a brief description of several of the more prominent models is given. These biological theories are then contrasted with two psychological theories of panic disorder. Discussion of these various theories will illustrate the utility of an animal model to address questions about panic disorder's etiology.

Biological Theories

Original theories for the onset of panic disorder were biologically based, largely because of the occurrence of spontaneous panic attacks (which suggest the occurrence of neurochemical events). Panic attacks resulting from the administration of biological challenge agents were also taken as evidence for a biochemical basis for panic disorder (Margraf & Ehlers, 1990).

Biological accounts for the cause of panic disorder implicate dysregulation in neurotransmitter systems, such as the noradrenergic (Charney, Woods, Price, et al., 1990), serotonergic (Kahn, Asnis, & Wetzler, 1988), cholecystokinin (Bradwejn et al., 1992), and the benzodiazepine/ GABA (Nutt, 1990; Nutt & Lawson, 1992) systems. Besides central neurotransmitter systems, a variety of other systems have been proposed as dysfunctional in panic disorder, including hypersensitive peripheral β-adrenergic receptors (Rainey et al., 1984), hypersensitive CO_2 chemoreceptors (Gorman & Papp, 1990) and a hypersensitive "suffocation alarm" (Klein, 1993).

The finding that agents such as sodium lactate and caffeine elicit panic does not, however, require that the basis for panic disorder be localized in aberrant biology. Studies have demonstrated similar physiological reactions to challenge agents in panic disorder and controls (Margraf, Ehlers, & Ruth, 1986; Beck & Berisford, 1992). The psychological reaction of subjects is, in fact, a better discriminator between groups than physiological reactions in most studies. The finding that psychotropic medication can reduce or eliminate panic attacks might be interpreted as support for a fundamental biological origin of panic disorder. However, relapse rates of 30-90% upon medication withdrawal (Roy-Byrne & Katon, 1987) do not require the conclusion that these medications are acting directly on the underlying mechanism of the disorder. Instead, the high relapse rate in panic disorder patients upon medication withdrawal suggests that the medications are simply suppressing the occurrence of feared symptoms.

Noradrenergic Dysregulation

Noradrenergic dysregulation has been suggested as a possible mechanism for panic disorder (Charney, 1990). Redmond and Huang (1979) stimulated the locus coeruleus of primates by electrical and pharmacological (piperoxane and yohimbine administration) means. The sympathetic activation created by the locus coeruleus is regarded as a negative feedback system, wherein increases in norepinephrine release trigger presynaptic inhibitory α-2 autoreceptors, which limit subsequent (NE) release. Yohimbine is an α-2-adrenergic antagonist that stimulates the locus coeruleus (Goldberg & Robertson, 1983). Yohimbine increases norepinephrine production from the locus coeruleus by inhibiting the feedback mechanism of the presynaptic α-2 adrenergic autoreceptor. The stump-tailed monkeys in Redmond and Huang's (1979) study displayed behavioral and physiological reactions that were nearly identical to those displayed when confronted with threatening stimuli, such as threats from conspecifics and humans. Results from studies involving yohimbine infusions along with pre-clinical work involving stimulation of the locus coeruleus have laid the foundation for the noradrenergic dysregulation theory (also know as the locus coeruleus model) of panic disorder (Charney, Woods, & Krystal, 1990; Charney, Woods, & Goodman, 1987). In it's original formulation, the locus coeruleus model assumed that panic disorder is the result of abnormally high responsivity in brain noradrenergic systems (Charney & Heninger, 1986).

The locus coeruleus model was reformulated from its earlier position that noradrenergic dysfunction is common to all patients by specifying that abnormality in noradrenergic systems may be characteristic of a distinct subgroups of patients (Charney & Heninger, 1986). Most biological models make the same assertion regarding dysfunction, namely that a subset of patients has a specific biological dysregulation. The α-2 adrenergic autoreceptor is the primary candidate for dysfunction in the reformulation of the locus coeruleus model. Charney, Woods, and Goodman (1987) reported a 54% incidence of panic in panic disorder patients following yohimbine administration, whereas only 5% of normal controls panicked. The effects of yohimbine in triggering panic attacks do not occur in major depressive disorder, generalized anxiety disorder, obsessive compulsive disorder, or schizophrenia (Charney, Woods, & Krystal, 1990). Because yohimbine does not trigger panic in these other disorders, its effects appear to be specific to panic disorder. Caffeine increases the rate of firing of the locus coeruleus in animals (Olpe, Jones, & Steinmann, 1983); therefore the noradrenergic dysregulation theory might explain the greater sensitivity of panic disorder patients to caffeine.

The primary shortcoming of the noradrenergic dysregulation model is its predictive validity. The locus coeruleus model predicts that drugs that increase locus coeruleus firing (such as buspirone and carbamazepine) should be profoundly anxiogenic. Contrary to this prediction, buspirone and carbamazepine actually have mild anxiolytic effects when given to panic disorder patients (Taylor, Eison, Riblet, & Van der Maelen, 1985; Cohn & Wilcox, 1986; Uhde et al., 1985). Furthermore, administration of mianserin, a drug which blocks α-2-adrenergic autoreceptors, may even relieve anxiety (Klein, Rabkin, & Gorman, 1985) in some patients, rather than producing panic. These criticisms should be qualified by the possible differences in the degree of locus coeruleus stimulation effected by carbamazepine, buspirone, and mianserin compared with yohimbine. Yohimbine may create greater NE output, or the locus coeruleus-mediated effects of these other drugs might be overshadowed by anxiolytic actions at other sites. The failure of clonidine as an effective treatment for panic attacks also argues against the locus coeruleus model. Since clonidine markedly decreases locus coeruleus firing, it should be markedly panicolytic, yet it is ineffective in treating panic (Hoehn-Saric, Merchant, Keyser, & Smith, 1981; Liebowitz, Fyer, & Gorman, 1981).

Serotonergic Dysregulation

Based on pharmacological, biochemical, and behavioral evidence, serotonergic (5-HT) neurons have been implicated in anxiety (Iverson, 1984). The two main lines of evidence implicating serotonin dysregulation in panic disorder are the efficacy of serotonergic drugs in the treatment of panic disorder and the panicogenic effects of direct and indirect acting serotonin agonists.

Metachlorophenylpiperazine ($^{m\text{-}}$CPP) is a serotonin agonist that directly stimulates postsynaptic receptors (Maser & Woods, 1990). $^{m\text{-}}$CPP shows the highest affinity for 5-HT_{2c} and 5-HT_3 receptors (Kahn & Wetzler, 1991; Shen, Monsma, Metcalf, & Jose, 1993; Hoyer, 1988).

Intravenous administration of 0. 1mg/kg of $^{m-}$CPP resulted in 45% of panic disorder patients versus 30% of controls experiencing a panic attack (Charney, Woods, Goodman, et al., 1987). Oral $^{m-}$CPP induced panic in 60% versus 0% of panic disorder patients and normal controls experiencing panic, respectively (Kahn, Wetzler, van Praag, & Asnis, 1988). Some studies have reported that $^{m-}$CPP induces significantly higher degrees of cortisol response in panic disorder patients compared to controls (Klein, Zohar, Geraci, Murphy, & Uhde, 1991; Kahn, Asnis, Wetzler, & van Praag, 1988), although another study failed to replicate this relationship (Charney, Woods, Goodman, & Heninger, 1987).

The effects of indirect serotonin agonists also have been examined in panic disorder patients. Two studies by Targum have examined the effects of fenfluramine in panic disorder (Targum, 1991; Targum & Marshall, 1989). Targum (1991) reported that about two thirds of panic disorder subjects reacted with extreme anxiety to this agent. Administration of serotonin precursors as a biological challenge agent also has been attempted. Infusions of both tryptophan and 5-OH tryptophan failed to produce panic. In fact, 5-OH tryptophan actually decreased anxiety slightly and produced sedation (Charney & Heninger, 1986; den Boer, 1990). Based on this pattern of biological challenge results, some investigators have concluded that at least a subset of panic disorder patients have hypersensitive post-synaptic 5-HT receptors (McNally, 1994).

The possibility that panic disorder is characterized by a dysregulation in brain serotonin is supported by the efficacy of serotonin specific reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) in treating panic disorder (Pecknold, 1990). SSRIs and TCAs both increase the synaptic availability of serotonin, eventually leading to down-regulation of the receptors (Cooper, Bloom, & Roth, 1996). Panic disorder patients typically exhibit a biphasic response to SSRIs and TCAs, at first becoming more anxious, then gradually improving (Kahn & Westenberg, 1985). The initial worsening of anxiety with SSRI and TCA treatment is consistent with post-synaptic receptor hypersensitivity. This initial worsening is thought to be similar to that created by direct serotonin agonists such as $^{m\text{-}}$CPP. SSRIs/TCAs initially produce anxiety because of a buildup in endogenous transmitter, rather that direct stimulation of receptors by a drug. The treatment with TCAs and SSRIs increases serotonin in the synapse, which, over a period of weeks, down-regulates serotonin receptors. Down-regulation of these receptors is thought to be responsible for the decreased anxiety.

The novel anxiolytic agent buspirone has some serotonin agonist properties, acting post-synaptically at high doses and pre-synaptically at low doses. Buspirone treatment reportedly exacerbates panic disorder (Frazer & Lapierre, 1987), although it is effective in treatment of generalized anxiety disorder (Goa & Ward, 1986). Buspirone's aggravation of panic disorder is consistent with the post-synaptic receptor hypersensitivity hypothesis, as it has some agonist properties (Taylor & Moon, 1991). Buspirone produces many unpleasant side effects, such as nausea, insomnia, and dizziness, which may be especially difficult for panic disorder patients to tolerate (Frazer & Lapierre, 1987).

Peripheral β-Adrenergic Receptor Hypersensitivity

Peripheral β-adrenergic receptor hypersensitivity has been considered as a possible mechanism for the etiology of panic disorder (Rainey et al., 1984). Several investigators (Frohlich, Tarazi, & Dustan, 1969; Easton & Sherman, 1976) have noted the similarity of symptoms of patients with β-adrenergic hypersensitivity and panic patients. In a double blind study of isoproterenol (a β-adrenergic agonist) infusions in panic disorder patients and normal controls, 63% of panic disorder patients but only 11% of control subjects panicked (Freedman, Ianni, & Ettedgui, 1984). Rainey et al. (1984) compared the effects of isoproterenol to lactate infusions, reporting that isoproterenol and lactate-provoked panic attacks were both similar to naturally occurring panic attacks (as rated by subjects). However, isoproterenol-provoked panics were generally less severe than attacks provoked by lactate. Hypersensitive β-adrenergic receptors also might explain the panicogenic effects of caffeine, as caffeine increases plasma epinephrine and norepinephrine in human subjects (Robertson, 1981).

The β-adrenergic receptor hypersensitivity hypersensitivity hypothesis of panic disorder was assessed by infusing low doses of isoproterenol to panic disorder patients and normal controls (Nesse, Cameron, Curtis, McCann, & Huber-Smith, 1984). The low doses of isoproterenol should have provoked stronger physiological reactions in the panic disorder patients if panic disorder patients' peripheral β-adrenergic receptors were hypersensitive. Contrary to prediction, the normal controls showed greater reactivity, implying that β-adrenergic receptors may in fact be down-regulated in panic disorder patients.

Isoproterenol's panicogenic effects are probably not a result of direct central effects because isoproterenol does not usually cross the blood-brain-barrier. Taken together, down-regulation of peripheral beta-receptors and the lack of crossover into the central nervous system suggest that biological models cannot account for isoproterenol's effects. Epinephrine's panicogenic effects in panic disorder patients warrant the same conclusion because also does not enter the CNS (Veltman, Zijdarveld, & Dyck, 1996).

Benzodiazepine/GABA Receptor Dysfunction

Nutt, Glue, Lawson, and Wilson (1990) hypothesized that panic patients may be characterized by a dysfunction in the GABA/benzodiazepine receptor complex. The benzodiazepine site binds agonist, antagonist, and inverse agonists. It has been hypothesized that panic disorder patients may have high levels of an endogenous inverse agonist such as diazepam binding inhibitor (DBI). Nutt et al. (1990) administered flumazenil (a benzodiazepine antagonist), which occupies but does not activate the benzodiazepine site) to panic disorder patients in an investigation of this possibility. Based on the elevated endogenous inverse agonist hypothesis, the effect of flumazenil was predicted to be anxiolytic in panic patients. Once administered, flumazenil produced panic attacks in 80% of panic disorder patients, while no controls panicked (Nutt et al., 1990). Another study reported that oral administration of flumazenil produced panic in 40% of panic disorder patients, whereas no normal controls panicked (Woods, Charney, Silver, Krystal, & Heninger, 1991).

The panicogenic effects of flumazenil might be explained by the existence of an endogenous anxiolytic, that is blocked to a greater degree in patients than in controls. Another possible explanation for flumazenil's effects involves changes in the benzodiazepine/GABA receptor. Nutt et al. (1990) suggested that the "set point" in panic disorder patient's benzodiazepine receptors is shifted in the inverse agonist direction. With such a "shift" in receptor functioning, antagonists (such as flumazenil) would act like inverse agonists and agonists, such as diazepam, would have less of an effect. The ineffectiveness of low potency benzodiazepines, and the high doses of high potency benzodiazepines such as alprazolam required to treat panic disorder is consistent with Nutt et al.'s (1990) hypothesis. Evidence for sub-sensitivity to benzodiazepine agonists has been reported. Panic disorder patients demonstrate lower reductions in plasma catecholamines compared to healthy controls (Roy-Byrne et al., 1989). Whereas β-carbolines (which are benzodiazepine inverse agonists) have been shown to produce marked panic-like reactions in healthy controls (Dorow, 1983; Gentil, 1990), no study to date has assessed panic disorder patient's reactivity to these compounds.

Carbon Dioxide Chemoreceptor Hypersensivity

Gorman and Papp (1990) have suggested that at least a subset of panic disorder patients are characterized by abnormally sensitive carbon dioxide (CO_2) chemoreceptors located in the medulla. These chemoreceptors are thought to monitor peripheral autonomic activity and to compare this activity with metabolic demand. Mismatches between metabolic demand and metabolic supply cause these receptors to stimulate the locus coeruleus which then initiates a panic attack (Gorman & Papp, 1990). If these chemoreceptors are hypersensitive, or some other brainstem regions in this system are malfunctioning, the result is panic. Within Gorman and Papp's (1990) model, limbic structures such as the hippocampus and amygdala are hypothesized to be the sites where the tonic levels of anticipatory anxiety observed in panic disorder patients originates (Gorman et al., 1989). The panicogenic effects of challenge agents such as sodium lactate, carbon dioxide, hyperventilation, and sodium bicarbonate have been explained in terms of the hypersensitive CO_2 chemoreceptor hypothesis.

The effects of carbon dioxide inhalation are obviously relevant to the carbon dioxide Chemoreceptor hypersensitivity theory. Inhalation of carbon dioxide has been repeatedly demonstrated to be a potent panicogen, provoking panic in patients with panic disorder patients more often than controls. Doses of CO_2 between 5 % and 35% reliably produce symptoms of panic (McNally, 1994). Many researchers have used a single breath of 35% CO_2 and 65% O_2 to elicit panic (van der Hout, 1988; Papp, Klein, & Gorman, 1993; Griez, 1990; Griez, 1987; van der Hout, 1985). Panic Disorder patients generally experience panic attacks at a rate of about 70% in response to 35/65 % CO_2/O_2 (Papp, 1993). In perhaps the first use of CO_2 as a challenge agent, Gorman et al. (1984) found that 5% CO_2 inhalation resulted in 58% of panic disorder patients having a panic attack, whereas only 25% of patients panicked while hyperventilating on room air. Hyperventilation produces respiratory alkalosis and hypocampnea (reduced CO2 tension in arterial blood), and inhalation of CO_2 produces acidosis and hypercampnea (increased CO2 tension in arterial blood). Although they have opposing physiological mechanisms, both procedures are known to produce panic more often in panic disorder patients than in control groups (van der Hout, 1988). In addition to CO_2 manipulations, the hypersensitive CO_2 chemoreceptor hypothesis also is frequently used as a potential explanation for the panicogenic effects of sodium lactate infusions.

Pitts and McClure (1967) first administered sodium lactate as a biological challenge agent in the late 1960s. In this classic study, 10mg/kg of sodium lactate produced panic in 93% of anxiety neurotics (a diagnostic forerunner of panic disorder), but only 12% of normal controls. Overall, approximately 70% of panic disorder patients respond to sodium lactate with panic, compared to few if any of the normal controls (Cowley & Arana, 1990; Liebowitz, Fyer, & Gorman, 1985). Sodium lactate is metabolized into bicarbonate, which increases peripheral pH and plasma CO_2 (Gorman, 1989). Sodium bicarbonate infusions also produce panic attacks, although to a lesser degree than does sodium lactate (45% versus 59%, respectively) (Gorman, 1989). Because both sodium lactate and sodium bicarbonate are metabolized into CO_2, hypersensitive chemoreceptors might account for the panicogenic nature of both of these agents in panic disorder patients.

Although the carbon dioxide chemoreceptor hypersensitivity hypothesis has intuitive appeal, evidence contrary to this hypothesis has recently been reported. D-lactate (an isomer of L-lactate) is panicogenic, yet is not metabolized into CO_2 (Nutt & Lawson, 1992). Additionally, bonnet macaques infused with sodium lactate show no increase in central CO_2 or lactate levels (Coplan, Gorman, & Klein, 1992). The findings from studies using D-lactate and sodium lactate in primates argue against the CO_2 chemoreceptor hypersensitivity hypothesis as a viable explanation for panic disorder.

A hypothesis related to the chemoreceptor hypersensitivity model is Klein's "suffocation alarm" hypothesis. According to Klein (1993), patients with panic disorder have a lowered threshold for an evolved "suffocation alarm." Rising serum levels of CO_2 and lactate normally associated with suffocation are the supposed triggers for the firing of this alarm. The abnormally lowered threshold for this alarm causes chronic hyperventilation, which is adaptive in that it lowers blood CO_2 levels. A central issue that Klein's hypothesis has yet to address is that the level of CO_2 needed to trigger the suffocation alarm is not specified. Inhalation challenges containing up to 875 times the amount of CO_2 contained in normal room air have been used. The finding that these challenges fail to produce panic attacks in almost 100% of panic disorder patients suggests that some other mechanism might be involved in the genesis of panic following CO_2 inhalation (McNally, 1994).

Caffeine and Panic

Caffeine is a xanthine derivative that is widely used as a psychotropic agent. Ingestion of low doses of caffeine increases alertness and decreases fatigue (Weiss & Laties, 1962). Although caffeine generally produces beneficial effects at low doses, higher doses can induce insomnia, anxiety, tachycardia, and dyspnea (Greden, 1974). Panic disorder patients are more sensitive to the administration of caffeine than controls (Uhde, 1990). Uhde (1990) reported that 37.5% of panic disorder patients panicked in response to an oral dose of 480 mg/kg caffeine, while no controls panicked. Larger dosages (10 mg/kg) of caffeine produced panic in 71% of patients but in no control subjects (Charney, 1985). The mechanism by which caffeine produces anxiety is unknown. Theories implicating inhibition of phosphodiesterase (Butcher & Sutherland, 1962), inhibition of adenosine (Snyder & Sklar, 1984), and increased CNS catecholamine activity (Berkowitz, Tarver, & Spector, 1970) have been advanced to account for caffeine-induced anxiety. The most likely explanation for caffeine's ability to trigger anxiety is its blockade of the adenosine receptor, because this effect occurs within the range of normally ingested doses (Shear, 1986; Snyder & Sklar, 1984). Inhibition of phosphodiesterase and increased CNS catecholamine activity occur only at doses that are outside the normally ingested range. The following findings argue against a specific link between panic disorder and caffeine. Patients with generalized anxiety disorder are as equally reactive to caffeine as panic disorder patients are (Bruce, Scott, Shine, & Lader, 1992). Normal controls with high scores on the anxiety sensitivity index respond to caffeine like panic disorder patients (Reiss et al., 1986).

Cholecystokinin Dysregulation

Bradwejn et al. (1992) suggested that panic disorder is characterized by cholecystokinin dysregulation. CCK, a peptide originally discovered in the gastrointestinal tract, is also found in significant concentrations in the central nervous system (Dockray, 1976). CCK probably functions as a neuromodulator or neurotransmitter within the central nervous system (Cooper, Bloom, & Roth, 1996).

Intravenous CCK-4 (a tetrapeptide) infusions produces anxiety and panic attacks in healthy volunteers (de Montigny, 1989) and panic disorder patients (Bradwejn, Kosztcki, & Shriqui, 1991). At a dose of 25μg, CCK-4 induced panic in 91% and 17% of panickers and controls, respectively. At 50μg, the infusion produced panic in 100% of patients and in 47% of the controls.

CCK-4 is one of the few biological challenge agents that has been administered across a range of doses to both panic disorder patients and healthy controls. The combined results of several studies using CCK-4 as a challenge agent (de Montigny, 1989; Bradwejn et al., 1992; Bradwejn, Kozynki, & Shirkiqui, 1991; Shlik et al., 1997) are presented in Figure 1. The figure presents dose-response curves for both panic disorder patients and healthy controls to CCK-4. As can clearly be seen, both panic disorder patients and healthy controls panic in response to CCK-4 infusion. However, the panic disorder patients are more sensitive. Up to 70% of normal controls panic in response to high doses of CCK-4 (de Montigny, 1989). The observation of greater sensitivity in panic disorder patients has been repeatedly made in past studies (McNally, 1994; Bradwejn et al., 1992; Bradwejn, Kozynki, & Shirkiqui, 1991). The parallel dose response curves for both groups are noteworthy because this implies that panic disorder patients' reactions to CCK-4 are quantitatively and not qualitatively different from healthy control's reactions. This distinction is critically important in panic disorder because it suggests a similar mechanism of action between panic disorder patients and healthy controls with only a difference in sensitivity to the agent separating the group.

Summary and Critique of Biological Models for Panic Disorder

Biological models as a group share conceptual flaws in their underlying premises. A problem with biological models of panic is that the disorder presents a relatively homogeneous behavioral profile, whereas these biological models propose a heterogeneous array of specific abnormalities. The marked diversity of neurotransmitter and neuroanatomical structures that have been proposed to be dysregulated in panic disorder is quite striking. In order to illustrate why so many systems have been proposed as dysfunctional in panic disorder, the general pattern for the development of biological models for panic disorder is described as follows:

1. Administer a drug to both panic disorder patients and healthy controls.
2. Observe higher rates of panic attacks in panic disorder patients compared to healthy controls.

3. Propose a *post hoc* explanation to account for the higher sensitivity of panic disorder patients to the agent, implicating the biological substrate affected by the agent administered (if the substrate is known).
4. Conduct further studies to empirically test predictions drawn from the new explanation.

Studies that demonstrate different panic rates between panic disorder patients and healthy controls following administration of a drug usually have been the origin of biological theories of panic disorder. The authors of these studies then propose a hypothesis to account for the data, typically speculating that the biological substrate affected by the agent (if known) is dysregulated. The new hypothesis implicates some physiological abnormality that panic disorder patients are proposed to have and the inference is drawn that this abnormality might be the underlying cause to panic disorder, or for at least a subset of panic disorder patients. The logical and empirical basis for the supposition that "subsets" of patients have specific biologic vulnerabilities is discussed below. Predictions drawn from the new hypothesis about other agents that should either provoke or prevent panic are then tested. As reviewed in detail above, specific hypotheses for a biological basis of panic disorder have generally received little empirical support when such tests have been conducted. Administration of agents such as carbamazepine (Taylor, Eison, Riblet, & Van der Maelen, 1985), D-lactate (Nutt & Lawson, 1992) and low doses of isoproterenol (Nesse et al., 1984) actually have provided evidence that directly contradicts their parent hypothesis.

As an exercise in examining the logical basis of these hypotheses, suppose one were to follow the pattern outlined above, administering minute doses of an irreversible acetylcholinesterase inhibitor such as sarin gas as a challenge agent. While this is an extreme example, it illustrates the mechanistic approach that has lead to the proliferation of biological hypotheses of panic disorder. One would predict that the panic disorder patients would show much higher panic rates compared with controls, especially if subjects are informed that they are inhaling very low concentrations of a nerve gas. Following the same logic that has led to many biological hypotheses of panic disorder, the next step in this process would be to explain the different responsiveness in terms of biological dysregulation. The proposal that a subset of panic disorder patients is characterized by a dysregulation in either peripheral or central acetylcholinesterase would perhaps be made. This *post hoc* hypothesis now purports to explain why panic disorder patients are more sensitive to acetylcholinesterase inhibitors, and one could make predictions that other drugs that inhibit acetylcholinesterase also will be panicogenic. In this example, it is likely that anticipatory anxiety plays a key role in generating panic attacks, perhaps by producing bodily sensations that patients are prone to fear.

Rather than adding a new transmitter substrate to the list of systems thought to be dysregulated in panic disorder, it would be useful to examine whether there is an alternative explanation. Psychological models of panic offer far more parsimonious explanations for the greater sensitivity shown by panic disorder patients to biological challenge agents, including the hypothetical example that was just presented. It might be reasonably argued that while there are indeed several biological hypotheses implicating dysregulation, a single biological dysregulation might eventually be found to underlie panic disorder. If this proves to be true, then the homogeneous behavioral profile of panic disorder would no longer be problematic. It is certainly possible that one of the biological models is indeed correct. However, a second conceptual flaw of biological models presented below argues against this possibility.

The supposition that "subsets" of panic disorder patients may have some biological abnormality is another conceptual flaw to biological models in general. The conception that "subsets" of patients may have the proposed abnormality is central to biological hypotheses, because their explanations for the results of biological challenge studies depend on this supposition. Before examining the evidence for these proposed subsets of panic disorder patients, the origin of the notion that there are "subsets of patients" with specific biological abnormalities should be clarified.

In the typical biological challenge study, not all of the panic disorder patients experience a panic attack in response to the challenge agent. For example, about 70% of panic disorder patients panic when given sodium lactate (Sandberg & Liebowitz, 1990). The fact that only some patients panic in response to biological challenge agents is the sole basis for the claim that within the larger population of panic disorder patients, a "subset" has the proposed abnormality. This finding suggests that those patients who do not panic do not have this abnormality, and healthy controls who do panic, by logical extension, also have the abnormality.

There seems to be an implicit acceptance of the validity of the idea that subgroups of panic disorder patients have at least one specific biological dysregulation (McNally, 1994). It is both premature and hazardous to accept this idea, because there is no convincing evidence for the concept. For example, it has not been shown that those subjects who panic in response to a challenge agent targeting a specific system remain constant over time. If the "subset" of patients or controls who panic in response to a specific challenge agent on one occasion is different from the subset who panic on later occasions, then the notion of subsets becomes less tenable. No systematic study of consistency of responses to challenge agents has been reported. Re-administration of a challenge agent to the same group of subjects has been done in a few studies (Keck et al., 1993; Yeragani et al., 1988). These studies have typically involved adding a treatment medication in order to assess whether the medication can prevent panic upon re-administration with the challenge agent and do not address this broader issue of categorization.

If there are subsets of patients with specific abnormalities, then it would be worthwhile to examine whether panic disorder patients can be categorized based on their responses to multiple challenge agents. If patients with a consistent vulnerability to lactate also have a vulnerability to yohimbine, but not flumazenil, then this finding would be useful to integrate these various biological hypotheses. Such sub-typing of panic disorder patients might lead to findings of differential response to therapies and differing etiological factors. No evaluation of multiple vulnerabilities has been reported. However, a few studies have examined the comparative panicogenic effects of two different challenge agents (e.g., Rainey et al., 1984; Ettedgui, 1984). If an aberrant biological vulnerability is actually the cause for a subset of panic disorder patients panicking, then the smaller subset of healthy controls who panic should also have the same biological vulnerability. This logical conclusion is typically not examined on theoretical or experimental grounds. If biological models are indeed correct, then studying this subset may prove quite fruitful.

Finally, the issue of serial precedence should be considered. Within biological models, the panic attacks that patients experience are attributed to a pre-existing biological dysregulation. It is also conceivable that a history of experiencing panic attacks is actually the cause of a biological dysregulation, if such dysregulation does indeed exist. The lack of prospective studies demonstrating that a biological dysregulation precedes the onset of panic disorder suggests that this possibility, as should not be dismissed. The plausibility of this possibility is supported by data from investigations of the learned helplessness effect. Studies of the physiological basis of the learned helplessness effect in animals suggests that the repeated experience of intense, uncontrollable and inescapable aversive events leads to actual changes in neurochemistry (Weiss, Stone, & Harrell, 1970). Panic attacks certainly are aversive and are often perceived as uncontrollable and unpredictable by patients (McNally, 1994). Therefore, they may indeed modify the neurotransmitter systems that have been implicated in panic disorder.

Overall, the datum supporting biological models of panic disorder are mixed. Some hypotheses have received support from studies using challenge procedures, only to later have predictions directly drawn from the hypothesis fail to support or contradict the hypothesis. Biological models of panic disorder have proposed an array of dysregulations to account for a disorder that has a homogeneous behavioral profile. These theories all rest on two unproven assumptions: 1) there are subsets of patients with specific (possibly multiple) vulnerabilities, 2) dysregulations are causal, rather than consequential to the onset of panic attacks. Given the tenuous status of biological explanations of panic disorder, it is possible that some other mechanism will account for the onset and maintenance of panic disorder. There are two other influential accounts for panic disorder, both of which can be characterized as psychological hypotheses.

Psychological Models

Cognitive Model

One of the most influential hypothesis for the etiology of panic disorder is the cognitive model of Clark (1986). This model views panic attacks as the result of catastrophic misinterpretation of bodily sensations associated with anxiety. The cognitive theory of panic disorder is often referred to as the catastrophic misattribution model. Within the cognitive model of panic disorder, bodily sensations or external stimuli can serve as triggers for a perceived threat. The patient then experiences apprehension regarding the perceived threat, which produces bodily sensations. It is the catastrophic misinterpretation of these bodily sensations that produces panic attacks (Clark, 1986, 1988). Contrary to the interoceptive conditioning model of panic disorder, bodily sensations are not triggers for a reflexive conditioned response of panic attacks. Instead, bodily sensations are one step in a positive feedback loop which culminates in a panic attack. For example, a patient climbing a set of stairs, might notice their heart beating faster than normal. The person perceives this rapid heartbeat as threatening and experiences apprehension. This apprehension produces bodily sensations of anxiety which are interpreted in a catastrophic manner (Clark, 1986, 1988). Examples of such cognitions would be "I'm having a heart attack" or "I'm about to die." The cognitive model for the onset of panic attacks is presented schematically in Figure 2.

Clark (1988) argues that biological challenge agents provoke panic attacks by exacerbating a biological dysfunction. Instead, panic disorder patients are simply responding with catastrophic misinterpretations to sensations produced by these agents. All biological challenge agents produce bodily sensations that might trigger these catastrophic misinterpretations. As biological challenge agents produce sensations and act on biological substrates, determining the cause of laboratory induced panic remains elusive.

Following biological challenges, panic disorder and healthy controls experience similar bodily sensations, yet only panic disorder patients respond with fears of dying or going crazy (Sanderson, 1988). This finding has been taken as support for cognitive theory. Additional support was provided by a study in which patients were given reassuring information regarding infusion of lactate. Reassuring information resulting in significantly lower panic rates in the group receiving reassurance (30%) compared to the group which received no reassurance (90%) (Clark, Salkovskis, & Anastasiades, 1990).

The cognitive model of panic proposes that once initiated, the panic sequence eventually culminates in a panic attack. There is a practical problem with this vicious circle formulation; namely, that there is no clear reason why panic attacks, once initiated, should cease. Once a panic attack occurs, it should produce strong physical sensations associated with anxiety that should also be catastrophically misinterpreted. The vicious circle should continue to spiral, growing stronger and stronger. The biological theories also fail to address the reason why panic attacks cease (Radomsky et al., 1998).

Contrary to cognitive model of panic disorder, Aronson, Whitaker-Azmitia, and Caraseti (1989) reported that laboratory-induced panic attacks can occur in the absence of cognitive misinterpretations. Rachman (1988) also reported that for the patients in his sample, a large percentage of panic attacks are not accompanied by fearful cognitions. In another study, catastrophic misinterpretations were found to be a consequence of panic attacks rather than preceding the attacks (Wolpe & Rowan, 1988). In each of these studies, panic attacks were not preceded by catastrophic misinterpretations, arguing against the necessity for misattribution of symptoms for panic onset. The occurrence of nocturnal panic attacks, and panic attacks triggered by relaxation also provide evidence against a purely cognitive theory for panic. Nocturnal panic typically erupts during non-REM sleep, and therefore is unlikely to be preceded by catastrophic misinterpretations (Craske & Freed, 1995; Craske & Barlow, 1989, 1990). Panic attacks triggered by relaxation occur fairly often (Cohen et al., 1985), yet are difficult to reconcile with cognitive model of panic, in that a perceived threat is difficult to identify.

In response to the criticism that some attacks are not preceded by catastrophic misinterpretations, Clark adjusted his model to include unconscious cognitions (Clark, 1988). Clark (1988) has adjusted his model to include unconscious cognitions (Clark, 1988). Clark (1988) has suggested that in some cases, catastrophic misinterpretations occur so fast and automatically that panic disorder patients do not perceive them. This supposition has justly drawn criticism, as it is nearly impossible to test whether these supposedly unconscious catastrophic misinterpretations do indeed occur, threatening the falsifiability of the cognitive model for panic disorder (McNally, 1994).

While the cognitive model of panic disorder has been highly influential and has inspired effective treatments, it has difficulties explaining many phenomena associated with panic disorder. The occurrence of panic attacks without fearful cognitions and the occurrence of nocturnal and spontaneous panic attacks (neither of which are preceded by catastrophic cognitions) compromise this model's validity.

Pavlovian interoceptive conditioning

The interoceptive conditioning conceptualization for the origin of panic disorder posits that conditioned fear to symptoms of bodily arousal cause panic attacks. In this formulation, the initial panic episode occurs as an unconditioned response as a result of a biological or psychological event such as hyperventilation or drug use (Goldstein & Chambless, 1978; Wolpe & Rowan, 1988). This initial panic attack typically occurs during periods of high stress and serves as an unconditioned response (UCR), becoming associated with the symptoms of bodily arousal which preceded the attack (Goldstein & Chambless, 1978; Wolpe & Rowan, 1988). These bodily arousal symptoms come to serve as conditioned stimuli (CS) for further panic attacks which occur as a conditioned reaction when exposure to internal sensations occurs. Examples of interoceptive cues that trigger panic include higher heart rate, palpitations, rapid respirations and shortness of breath (Acierno, Herson, & Van Hasslet, 1993). A schematic adaptation of the interoceptive-conditioning model of panic disorder is presented in Figure 3.

The interoceptive conditioning model is similar to the cognitive model of panic in many ways. Both models hold that the occurrence of bodily sensations triggers panic attacks and both view panic attacks following biological challenges as the result of reactions to challenge-induced bodily sensations. The interoceptive conditioning and cognitive models share the view that panic disorder patients do not have a biological dysregulation (Goldstein & Chambless, 1978; Wolpe & Rowan, 1988). In contrast to the cognitive model, the interoceptive-conditioning model holds that cognitions do not play a causal role in panic disorder (Goldstein & Chambless, 1978; Wolpe & Rowan, 1988).

The interoceptive conditioning model of panic disorder has been criticized by researchers who claim that the conditioned stimulus and conditioned response are qualitatively identical (Reiss, 1988; McNally, 1990). According to these critics, the "low level of arousal" as a conditioned stimulus triggers the conditioned response of "increased arousal." Additionally, the first panic attack is cited by one critic (McNally, 1990) as serving as both the UCS and the UCR, a situation which requires the UCR to elicit itself (if the UCR is a panic attack). These criticisms are, however, based on misunderstandings of the conditioning model of panic. Within the interoceptive conditioning model, panic attacks are both the unconditioned and the conditioned responses, but not the unconditioned stimulus (Goldstein & Chambless, 1978; Wolpe & Rowan, 1988). The UCS within the interoceptive conditioning model is the phenomenon of hyperventilation-induced dyspnea, which leads to panic (the UCR). Other stimuli besides dyspnea can serve as a UCS that triggers the initial panic attack, such as cocaine, LSD, withdrawal from psychotropics and various medical conditions (Acierno, Herson, & Van Hasslet, 1993). Regardless of the cause for the initial panic episode, the conditioning model proposes that interoceptive stimuli present before this first panic attack may acquire the ability to elicit panic (Acierno, Herson, & Van Hasslet, 1993). The primary criticisms of the interoceptive conditioning model for panic have centered on the ambiguity of the UCS (Sanderson & Beck, 1989; McNally, 1990, 1994). Of relevance to this point, it should be noted that recently conditioning theorists have contended that exposure to an identifiable environmental UCS is neither necessary or sufficient to initiate fear conditioning (Carter & Barlow, 1995; Forsyth & Eifert, 1996).

The "Learned Alarm" model of panic disorder is conceptually related to Goldstein and Chambless (1978) and Wolpe and Rowan's (1988) account for panic disorder (Barlow, 1988). The Learned Alarm model is presented in Figure 4. This model adds several variables to the classical conditioning account for panic onset, such as biological vulnerability, psychological vulnerability, and agoraphobic avoidance (Barlow, 1988). Within the Learned Alarm model of panic onset, the aversive event is the experience of a panic attack which serves as the UCR. This panic attack (a false alarm within this theoretical framework) becomes associated with bodily sensations that preceded the attack. Later panic attacks (learned alarms) are triggered by exposure to bodily sensations. A fundamental difference between the interoceptive conditioning model and the learned alarm model is that the later does not specify a UCS.

The interoceptive conditioning model contends that panic attacks following biological challenge agent administration are the result of conditioned fear of bodily sensations produced by biological challenge agents. Besides accounting for biological challenge agent-induced panic attacks, the interoceptive conditioning model can account for many other phenomena associated with panic disorder. Interoceptive conditioning can be used to account for the occurrence of spontaneous panic attacks and relaxation-induced panic attacks. The occurrence of spontaneous panic attacks has been cited as evidence against a cognitive account of panic disorder (McNally, 1994). Spontaneous panics are distinguished by the absence of external cues or catastrophic thinking, however, these episodes may be preceded by bodily sensations which occur inside or outside of awareness. The interoceptive conditioning model can thus easily provide an explanation for so-called "spontaneous" panic attacks. According to the interoceptive conditioning model, spontaneous panic attacks are caused by the occurrence of bodily sensations that the patient is not aware of, triggering a conditioned response. Bodily sensations acting as conditioned stimuli may also be a viable explanation for the paradoxical occurrence of "relaxation-induced panic attacks." As relaxation is typically accompanied by bodily sensations (Cohen et al., 1985), patients who have a conditioned fear of interoceptive cues might experience attacks following relaxation. Whether as conditioned fear cues, or as the subject of catastrophic misinterpretations, bodily sensations hold a central place in each of the psychological models for the onset of panic disorder.

Summary of etiological models

Both biological and psychological accounts for panic disorder have been advanced. For the past two decades there has been dispute as to the cause of panic disorder. While the present review suggests that interoceptive conditioning has the widest breath of explanatory power, no consensus in the field exists as to whether classical conditioning plays a role in panic disorder (McNally, 1994; Sanderson & Beck, 1989). The specific biological models of panic have generally encountered some findings that are inconsistent with their suppositions, and all rest on unsubstantiated claims that "subsets" of panic disorder patients are characterized by biological dysregulation. Additionally, biological models presuppose that these hypothetical dysregulations precede the onset of panic attacks--a supposition that has not been empirically studied. It may be just as likely that the experience of panic attacks can lead to dysregulations across multiple neurotransmitter systems. The biological challenge literature provides psychopathologists with a perplexing quandary. Biological challenge agents act on some biological substrate, yet also cause bodily sensations. These bodily sensations may be catastrophically misinterpreted, triggering panic attacks. It is also possible that panic attacks following biological challenges are a classically conditioned response, being elicited by bodily sensations. While ingenious studies have demonstrated laboratory induced panic attacks can be mediated by situational variables (Clark et al., 1990; Sanderson et al., 1989), the question of what causes panic attacks remains unanswered. Developing an animal model to answer this important question would be a potentially fruitful endeavor. It is possible that the conditioning model and some of the biological models could be constructed using non-human animals as subjects. The following section reviews and comments on animal models of panic attacks that have been attempted.

ANIMAL MODELS FOR SITUATIONAL PANIC ATTACKS

Animal models avoid many of the potential confounds of human studies, including life history, behavior, biochemical states, and wide genetic variability (Telner, 1984). Advantages to animal modeling in psychopathology also include the ethical acceptability of physiological, pharmacological, and chromosomal manipulations (e.g., knock-out/transgenic strains) that are not possible with human subjects (Suomi, 1989). McKinney and Bunney (1969) recommend that an animal model resemble a psychiatric condition in terms of etiology, biochemistry, symptomatology and treatment.

The primary criterion by which an animal model of psychopathology is judged is its validity. Evaluations of the validity of animal models typically follow three lines: face validity, predictive validity, and construct validity (Willner et al., 1992; Willner, Muscat, & Papp, 1992; Harris, 1989). Predictive validity refers to the model's sensitivity to drug challenges. To establish predictive validity, drugs or behavioral manipulations that alleviate a condition in humans should have a parallel effect in the model. Likewise, manipulations that exacerbate the condition in humans should have an opposite effect on the animal model. Face validity refers to the phenomenological similarities between the model and some aspect of the disorder. Construct validity refers to the degree that the cause of behavioral change in the animal is sufficient to cause a similar response in man (Triet, 1985; Sanger, 1991). Models can have different levels of each type of validity. For example, an animal model may have little face or construct validity, but possess high predictive validity. Such a model would be quite useful from a practical standpoint, as a means of screening new medications . However, it does not allow one to answer the questions regarding the etiology of a disorder to be examined. Etiology is addressed by the construct or face validity of the model. Animal models usually possess face validity for a specific facet of a disorder, such as a symptom or a cluster of symptoms. It is unlikely that any one animal model will be able to adequately encompass all the behavioral features associated with a psychiatric disorder.

The models that are reviewed attempt to create behavioral analogs of situational panic attacks and have varying degrees of face validity. In this overview, models are differentiated based on whether they employ interoceptive or exteroceptive stimuli. To date, no paradigm models the full range of symptoms that comprise panic disorder.

Models of Panic attacks based on exteroceptive stimuli

Mouse Defense Test Battery

The Mouse Defense Test Battery (MDTB) is an ethnologically-oriented model of panic attacks based on the flight/escape response that mice emit when confronted with a predatór (Griebel, Blanchard, & Blanchard, 1996). The MDTB involves placing mice in a runway and then exposing them to a hand-held rat, which is a natural predator (Griebel et al., 1995). This rat was brought progressively closer to the mouse until contact is made or the mouse flees. Dependent measures included the distance that the mice runs and the number of times the mice flees after exposures to the rat. Additionally, the mouse is "chased" by the hand-held rat, and the speed of the mouse is recorded (Griebel et al., 1995).

A wide range of drugs has been evaluated in the MDTB paradigm. Acute imipramine (a tricyclic antidepressant) and fluoxetine (a serotonin specific reuptake inhibitor) administration increased avoidance distance and frequency (Griebel et al., 1995), a finding consistent with clinical reports of the exacerbation of panic attacks when beginning treatment with SSRIs (Westenburg & Dern Boer, 1993).

Acute injections of alprazolam and chlordiazepoxide at non-sedative dosages failed to reduce the distance fled or speed at which mice ran. This effect was in contrast to the reduction in distance fled seen when alprazolam was chronically administered. Flumazenil (a benzodiazepine antagonist) and RO 19-4603 (a benzodiazepine inverse agonist) significantly increased the avoidance distance in mice when tested. Flumazenil's increasing avoidance in this model is consistent with it's panicogenic effects in panic disorder patients (Nutt et al., 1990).

There are several types of serotonin (5HT) receptors, many of which are selectively targeted by certain anxiolytic agents. The $5HT_{1A}$-receptor agonist buspirone is ineffective in treating panic disorder (Frasier & Lapretere, 1987; Norman & Judd, 1989). Consistent with the clinical findings of ineffectiveness of $5HT_{1A}$ agonists in treating panic disorder, 8-OH-DPAT (a full $5HT_{1A}$ agonist), and gepirone (a partial $5HT_{1A}$ agonist) failed to demonstrate efficacy in this model.

The MDTB appears to be an effective screening model for anti-panic compounds. The model possesses adequate face validity as a reproduction of acute avoidance that is panic-like, especially considering that panic attacks are often accompanied by an "urge to escape" (APA, 1994, p. 394).

While this model possesses elements of face validity as a reproduction of acute avoidance behavior, its construct validity is lacking. The model essentially represents the responses of normal mice confronted with a predator. The flight responses of the subjects are modulated by the administration of pharmacological agents. By analogy to humans, the mice are essentially normal controls exposed to a threatening situation. Data from this model suggest that if healthy controls were pretreated with an anxiogenic or anxiolytic agent before being confronted with threatening stimuli, they would demonstrate greater and lesser escape behavior, respectively. In order to make this model more relevant to panic disorder, one would need to show different sensitivity levels in different subgroups of mice. Manipulations that might produce higher sensitivity include sensitization of neuroanatomical structures involved in emotion, exposure to uncontrollable aversive events such as shocks, or classical conditioned fear of bodily sensations. Demonstrating that a subgroup of mice that, following some manipulation, are more reactive to the drugs tested compared with controls would provide a model of panic disorder with greater construct validity.

Conditioned Ultrasound Distress Vocalizations

A recent animal model of panic attacks is the conditioned ultrasound distress vocalizations (USV) procedure (Molewijk, van der Poel, Mos, van der Hayden, & Oliver, 1995). Adult rats may produce ultrasonic distress vocalizations (USV) in the presence of a predator (Blandchard, Blanchard, Agullana, & Weiss, 1991), a dominant male (Van der Pool & Miczek, 1991), or after either a loud (Katt & Wasser, 1991) or painful (Tonouge, 1986) stimulus. Based on these findings Molewijk et al. (1995) proposed the USV paradigm as a model for panic attacks. Molewijk et al. (1995) placed rats in a circular Plexiglas cage on top of a gridfloor connected to a shock generator. Rats were exposed to inescapable shocks on two occasions while in this cage to form an association between the cages and shocks. Following these conditioning trials, reintroducing rats into the cages resulted in the emission of large numbers of distress vocalizations (USV) which served as the measure of panic-anxiety (Molewijk et al., 1995). The ability of drugs to modify USV output was assessed in later test sessions.

A variety of pharmacological agents were administered to different sub-groups of rats, including diazepam, chlordiazepoxide, alprazolam, flumazenil, imipramine, buspirone, clonidine, desipramine, clomipramine, yohimbine, and haloperidol. Buspirone, ipsapirone, flesinoxin, and 8-OH-DPAT (all $5HT_{1A}$ agonists) strongly reduced USV in treated animals. The $5HT_{1A}$ agonist buspirone has, however, been found to be ineffective in the treatment of panic-related anxiety, and even increases anxiety in some cases (Robinson & Shrot, 1989). Alprazolam (an effective anti-panic agent) and haloperidol (a dopamine antagonist), produced similar profiles. Both drugs reduced USV only at high doses, and only at doses which reduced locomoter activity. The finding that alprazolam produced a profile that was nearly identical to a drug serving as a negative control (haloperidol) suggests this model has poor predictive validity. Furthermore, the benzodiazepine antagonist flumazenil had no effect of USVs, yet is panicogenic when administered to panic disorder patients (Nutt et al., 1990). Contrary to these negative findings, some support for the predictive validity of the model was found in the reduction of USV by imipramine (a 5HT/NA- uptake inhibitor) and the 5HT-reuptake-inhibitors fluoxamine and clomipramine.

The α-2-adrenergic agonist, clonidine, as well as the α-2 adrenergic antagonist, yohimbine, both reduced USV in this paradigm. Clonidine has been reported to have minimal efficacy in the reduction of panic anxiety (Uhde et al., 1989) and fails to block lactate-induced attacks in the majority of panic patients who previously panicked under lactate (Coplan, 1992). The fact that both clonidine (which does not affect panic-behavior) and yohimbine (which is a potent panicogen) reduced USV in the model argues against a homologous pharmacological profile of the USV model and panic disorder.

The USV model seems to possess some face validity as a model for situational panic attacks; however, it has low predictive validity. The USV procedure also lacks construct validity as a model for panic disorder. Molejiwk's (1995) procedure produces a conditioned fear of a context (as measured by USV). This model is more consistent with the disorder of specific phobia (situational type). Extending the findings of this model to humans essentially implies that a person with a specific phobia (e.g., bridges or heights) would be less fearful of the feared contextual cues if they were pretreated with a sedative, or more fearful if given a panicogenic agent. The relevance of the model to panic disorder, which is characterized by fear of bodily sensations, is questionable.

Demonstrating that a subgroup of rats subjected to a procedure or manipulation thought to cause panic in humans caused this subgroup to exhibit higher sensitivity to panicogenic agents (measured by USVs) would be a more appropriate model of panic. If within this subgroup of more sensitive rats panicolytic agents eliminated the heightened sensitivity to panicogenic agents, then a homologous profile would have been demonstrated.

Flooding

Another proposed animal model of panic attacks is the "Flooding" model of Baum (1986). This procedure consists of exposing rats to a grid floor which has been previously associated with foot shocks and examining the rat's behavior (Baum, 1986). The box initially allows rats to escape footshock via climbing onto a retractable ledge. When placed back into the conditioning apparatus, the rats typically engaged in a pattern of behaviors characterized by attempts to climb on the now retracted ledge, and jumping towards the ceiling of the box. Other behaviors associated with exposure to the conditioning chamber are freezing, exploratory activity and grooming. When rats are exposed to the conditioning chamber and the avoidance response is prevented (i.e., flooding session), extinction of the shock avoidance behavior gradually develops (Baum, 1970, 1976). This model has been used as an animal analog to exposure therapy in man (Marks, 1972).

Baum and colleagues (1970) have demonstrated that pharmacological and environmental manipulations reduce the avoidance behaviors. Administration of chlorpromazine (Baum, 1973) or a peripheral muscle relaxant (Baum, 1985) reduced escape-oriented behaviors.

Environmental manipulations that have been used to decrease avoidance behavior include the presence of rats with no shock history in the apparatus (Baum, 1969) as well as loud noise during the flooding session (Baum & Gorman, 1970). The presence of rats without a history of being shocked in this context (termed "social facilitation") in the apparatus sharply reduced the avoidance behavior in the rat with a history of shock. Loud noises were not as efficacious as social facilitation or drugs on reducing the avoidance responses; however, did produce a significant decline in these behaviors (Baum, Pera, & Leclerc, 1985).

Baum's model has not been used in date to test the effectiveness of anti-panic drugs (imipramine, alprazolam, etc.), so the predictive validity of the model for anti-panic agents remains to be assessed. The finding that non-panicolytic agents (e.g., chlorpromazine) reduce avoidance responses suggests that the predictive profile, if fully evaluated, will be of poor specificity to panic disorder.

Face validity for the flooding model as an analog for panic attacks is partially substantiated by the similarity in escape-oriented behaviors that panic patients engage in when confronted with certain stimuli previously associated with panic attacks. Like the Conditioned USV procedure, however, the flooding model is best considered as a model for specific phobias of situations. The flooding paradigm produces conditioning to contextual stimuli, and then models extinction of avoidance. It is unclear how this model relates to panic disorder, other than as an analog of panic disorder patients' avoidance of situations previously associated with panic. The avoidance of feared situational contexts is a symptom of nearly all anxiety disorders, including specific phobia, social phobia, post traumatic stress disorder, panic disorder, and agoraphobia (APA, 1994).

Models of Panic Attacks Based on Interoceptive Stimuli

Non-human Primate Models

Freedman, Ianni, and Ettedgui (1987) have proposed a model of "Panic Disorder" based on subcutaneous administration of sodium lactate in non-human primates. The authors based this model on the observation that sodium lactate infusion induces cognitive, emotional, and measurable physiologic complaints of panic attacks in humans with panic disorder (Lebowitz, 1984, 1985). The experimental reproduction of "Panic anxiety" was accomplished by administering sodium lactate to eight macaque subjects via subcutaneous injection. Subcutaneous administration of sodium lactate was chosen because it mimics the onset of intravenous infusion, but does not require that the primate be restrained other than for a brief period. The behavioral reactions of the macaques to the effect of either the lactate or vehicle injection was observed and rated according to a taxonomic rating survey that divides behavior into two categories. The first category includes behaviors such as pacing, rolling, and fidgeting. Freedman et al. (1987) refer to this category of behaviors as " general arousal." The second category, termed "affective distress," is made up of behaviors such as startling, avoiding partners, self-clasping, and yawning (Freedman et al., 1987). Freedman et al. (1987) propose that these "affective distress" behaviors are analogous to panic-like anxiety in humans.

On the combined index of affective arousal and general arousal, the eight macaque males (that were each tested individually) showed a uniform pattern of significantly higher lactate verses vehicle scores. This uniformity broke down when "arousal" measures were separated from "affective distress." When the general arousal behaviors were separated from the affective distress behaviors, only 63% responded with greater affective response to lactate verses vehicle trials (e.g., a panic-like reaction as defined by the authors).

Freedman et al. (1987) then took three of the male macaques and administered chronic oral imipramine, with four other males receiving placebo. These macaques were then retested with sodium lactate. Pretreatment with imipramine resulted in affective distress levels comparable to vehicle treatment levels, while the placebo administered group had essentially no difference in their lactate response compared to their previous responses.

In a more recent study by Freedman's laboratory, oral yohimbine was administered to unrestrained bonnet macaques (Rosenblum, Coplan, Friedman, & Bassoff, 1991). In this study, there was no linear dose-response relationship between yohimbine and a behavioral scoring index. The subjects alternated between periods of activation (e.g., startle, freezing, frenzied pacing) and enervation (e.g., lying down, leaning against the wall, sighing). Neither of these behavioral patterns was deemed similar to panic-like anxiety by the investigators. Other work on primates has involved intravenous infusions of yohimbine and resulted in a dose-responsive increase in panic-like responses. These subjects were chair-restrained, and the route of administration was different, making direct comparison of these studies difficult. Another study of panicogenic drug effects in primates was conducted with pentagastrin (Rupnick, Schaffer, Siegel, & Iverson, 1993). Rupnick, Schaffer, Siegel, and Iverson (1993), administered the agent pentagastrin, which has been shown to possess pancogenic properties in man (Abelson & Neese, 1990) to rhesus monkeys. The results of the study indicate that pentagastrin, as well as CCK-4, failed to elicit behavioral or cardiovascular changes in the monkeys. This finding suggests that CCK induced panic-like effects may not be demonstrable utilizing pentagastrin or CCK-4 as challenge agents with rhesus monkeys.

The administration of sodium lactate to macaques has been advanced as a model of panic disorder. However, it is questionable whether this model meets criteria as a model of panic attacks, much less the full syndrome of panic disorder. A strong point of this model is imipramine's effectiveness in reducing lactate-induced "anxiety" in these macaques. This effect parallels imipramine's ability to block lactate-induced panic attacks in panic disorder patients (Frye, Lebowitz, Gorman, & Klein, 1985).

The general criticisms of the other models are applicable to the primate model as well. The primate model is essentially a demonstration of a dose-responsive relationship between some anxiogenic drugs and panic-like behavior in normal primates. The fact that differing anxiogenic drugs failed to produce anxiety argues that this model has poor predictive power. No ties to theories for the etiology of panic can be drawn, save for the supposed effects of these drugs triggering anxiety as a result of activation of a specific brain region. Even with this tie, the primate model still assesses normal monkeys and shows only that if humans without panic disorder (e.g., healthy controls) were given these agents, some would exhibit signs of anxiety. The finding that some human healthy controls panic in response to biological challenge tests has been repeatedly reported, again raising the question of what this model adds to our understanding of panic disorder. Imipramine's blocking panic-anxiety upon reinfusion of sodium lactate in these monkeys indicates that if human normal controls that panic at moderate doses of sodium lactate were treated with imipramine, they would likely show less anxiety if re-administered sodium lactate.

Electric Stimulation Of The Dorsal Periaqueductal Gray

Jeneck, Moreau, and Martin (1995) have proposed one of the most recent animal models of panic attacks based on pre-clinical and clinical literature on effects of electrical stimulation of the dorsal periaqueductal gray (dPAG). Electrical stimulation of the dPAG produces acute flight and escape, as well as autonomic changes that are similar to those elicited following exposure to stressful stimuli (Olds & Olds, 1963; Martin, 1976; Adams, 1979). Stimulation of the dPAG in humans results in similar physiological reactions (e.g., tachycardia, sweating, piloerection) but also produces sensations of intense anxiety and terror (Nashold et al., 1969). Jeneck et al. (1995) used dPAG stimulation as an aversive stimulus in an escape paradigm with rats. Movement between chamber compartments terminated stimulation of the dPAG. The threshold frequency that occasioned escape and the latency to escape were the dependent measures of anxiety.

After determining baseline frequency threshold and latencies, Jeneck and colleagues (1995) examined the effects of panicolytic (alprazolam, clonazepam) and panicogenic agents (yohimbine, caffeine) on escape. Both alprazolam and clonazepam produced increases in frequency thresholds, suggesting an anxiolytic effect. Yohimbine and caffeine produced decreases in frequency thresholds, suggesting an anxiogenic effect. The dPAG stimulation paradigm offers many features as an analog to human panic attacks, including autonomic arousal, and similarity between human dPAG neurostimulation and human panic attacks.

The extent that the drugs tested alter locomoter activity is unknown, representing a potential confound to the validity of this model. Increased locomoter activity could bias the dependent measures in an anxiogenic direction, while decreased locomoter activity would produce an opposite effect. Yohimbine produces increased or decreased locomoter activity in rats depending on the dose, route of administration, and behavioral outcome measure (Bowes et al., 1992). Findings from the dPAG stimulation model should be viewed with caution until the locomoter effects of drugs can be dissociated from the effects on anxiety.

An advantage of this model is the production of acute escape behaviors and autonomic arousal. However, a weakness is that it lacks adequate predictive validity. The 5HT$_{2A/C}$-receptor blocker trazadone increased frequency thresholds for dorsal PAG stimulation (Jeneck, 1989), yet has minimal effectiveness in the treatment of panic disorder (Charney, 1986). The challenge agent $^{m-}$CPP (which is anxiogenic in humans) reduced anxiety (Jeneck, 1989)-- an outcome which is opposite to $^{m-}$CPP's effects in panic disorder patients (Charney, Woods, & Gorman, 1987).

The dPAG stimulation procedure is interesting, especially because this procedure might be activating a neural substrate of panic attacks. The procedure is insufficient as a model for the study of panic disorder, because important symptoms of panic disorder are not addressed, such as the fear of bodily sensations and spontaneous panic attacks. Extending the finding to humans, the model suggests that dPAG stimulation in non-panic disorder patients would produce panic-like reactions, a finding already demonstrated in the report of Nashold et al. (1969).

Gamma-Aminobutyric Acid Blockade In The Dorsomedial Hypothalamus

Blockade of gamma aminobutyric acid binding in the doromedial hypothalamus (DMH) has been proposed as a model of panic disorder. This procedure involved infusion of bicuculline methiodide (a $GABA_A$ antagonist) into the cardiostimulatory region of the DMH of rats (Shekhar, 1994). Bicuculline methiodide infusion potently reduces $GABA_A$ neurotransmission by preventing activation of GABA receptors. GABA blockade in the DMH results in a cluster of responses that are phenomenological similar to human panic attacks. These similarities include increases in blood pressure, heart rate, respiration rate, "escape"-oriented behavior (Shekhar & Dimico, 1987), plasma catecholamines (Wible, 1989), and plasma ACTH (Dimico, Soltis, Anderson, & Wible, 1992). Additionally, electrical stimulation of the DMH in humans results in severe anxiety (Halgren, Walter, Cherlow, & Crandall, 1978).

Shekhar evaluated the effect of DMH stimulation on the social interaction of rats. Social interaction is thought to be a measure of anxiety in rats, with decreased social interaction reflecting anxiety and increased social interaction representing an anxiolytic effect (File, 1980). The effect of bicuculline at baseline and following treatment with two anti-panic agents (imipramine and clonazepam) was assessed. Bicuculline decreased social activity in the social interaction task (i.e., increasing anxiety). When rats were re-tested with bicuculline, chronically administered imipramine and clonazepam partially blocked bicuculline's effect, suggesting an anxiolytic action.

Unfortunately, a different profile exists following treatment with imipramine in panic disorder patients. Initial treatment imipramine in panic disorder patients is known to increase anxiety, with the panicolytic effects occurring only after several weeks of treatment (Westenburg & Der Boer, 1993). The ability of imipramine to increase social interaction with only one week of treatment suggests that it does not parallel imipramine's effects in human panic disorder patients.

Although the authors conclude the model is analogous to panic disorder, this is a liberal extrapolation not warranted by the current data. The model has some face validity for panic attacks (e.g., increases in heart rate, increased respiration, increased anxiety), but the paradigm is insufficient as a model of panic disorder. Numerous behavioral facets of panic disorder are absent from this model, such as the fear of bodily sensations, agoraphobic avoidance, spontaneous panic, and nocturnal panic attacks. There is no theory specifically implicating GABA dysregulation within the DMH. Therefore the construct validity of the model is suspect. The predictive validity of the model has yet to be adequately examined, because only anti-panic agents have been tested.

Summary Of Animal Models For Panic Attacks

Attempts to produce an animal analog to panic disorder are a difficult but worthy endeavor. It is unlikely that any one model will function as an analog for the full syndrome of panic disorder, because this requirement would necessitate reproducing such phenomena as spontaneous panic attacks and thought processes that occur during panic. The first of these phenomena would be extremely difficult to measure in non-human animals and the second would be impossible. The creation of mini-models which simulate some subset of symptoms of panic disorder is perhaps the most realistic outcome that can be accomplished. The models presented above have varying degrees of face validity and some have excellent predictive validity as well. Occasionally, models have been presented as analogs for panic disorder but are, at best, models for situational panic attacks.

While each model was individually critiqued after being presented, it is instructive to examine the validity all of these models at a broader level. The criticism of these models consistently made the general assertion that models, to date, are analogs of situational panic attacks in healthy controls and not analogs to panic disorder. The simplest example of this is the primate model, in which primates are administered a panicogenic agent and a percentage of the primates displayed behaviors that the researchers likened to panic. The finding that sodium lactate elicits greater panic attacks in human healthy controls compared to vehicle is to be expected. What the finding of sodium lactate producing anxiety-like behaviors in primates adds to our knowledge of panic disorder is unclear. Indeed, it should be expected that anxiogenic drugs will produce anxiety-like behaviors in most animal species if one has an accurate measure for this behavioral reaction. The primate model lacks any construct validity as a model of panic disorder and is more appropriately considered a model for healthy control's reactions to paniciogenic agents.

In order to examine the construct validity of these models as a whole, it is helpful to examine at the most basic level what the models presented earlier have demonstrated. Generally, these models have examined reactions following exposure to an aversive stimulus (context associated with shock, predator, aversive brain stimulation) and determined whether these reactions can be modulated by the administration of anxiogenic or anxiolytic drugs. The primate model is an exception to this pattern, because the aversive stimulus is the drug itself. The reactions of subjects to the dPAG stimulation, BMI injection into the DMH, MDTB, USV, and flooding models can all be discussed in terms of response to aversive events. In the dPAG and BMI/DMH models, the aversive event is brain stimulation, whereas in the flooding and USV models, the aversive event is exposure to a context previously associated with shocks. The MDTB utilizes exposure to a natural predator as the aversive stimulus. The finding that anxiogenic drugs can intensify behavioral reactions to threatening situations is hardly surprising. It is reasonable to expect that healthy controls pretreated with a high dose of either caffeine, yohimbine, or sodium lactate before threat exposure will show greater reactivity. Heightened self-reported anxiety, increased tendency to flee the testing situation, and a corresponding increase in autonomic responses would be likely consequences of such pretreatment. These models are all variations on this theme of administering a threatening or aversive stimulus and assessing modulation of behavioral reactions with drugs. Therefore, each of these models contributes to our understanding healthy control's reactions to threat but contributes little with regard to our understanding of panic disorder.

NOVEL ANIMAL MODEL FOR THE FEAR OF INTEROCEPTIVE CUES

The animal models reviewed above have varying degrees of utility in screening of pharmacological anti-panic agents. None of the models reviewed has explored an etiological theory for the onset of panic disorder. Screening for efficacious medications to treat a disorder is a worthwhile enterprise; however, animal models can also be constructed to answer questions regarding the validity of etiological theories. The review of etiological models presented earlier suggests that a likely pathway for the onset of panic disorder is classical conditioning. To reiterate and summarize this account, patients develop a conditioned response of experiencing panic attacks in response to interoceptive bodily sensations of arousal. Surprisingly, no attempt has been made to create an animal model of panic disorder based on conditioned fear of bodily arousal. The fact that classical conditioning may be etiologically responsible for the majority of cases of panic disorder underscores the need for the development an animal model to test this model. While the classical conditioning model of panic has inspired effective treatments (McNally, 1994), intense controversy regarding interoceptive conditioning's role in the etiology of panic disorder remains.

The following section of this manuscript describes an animal analog of panic disorder based on the interoceptive conditioning model of panic. This master's project includes two laboratory experiments. Experiment 1 investigated the ability of epinephrine to function as a conditioned stimulus in a conditioned suppression paradigm. Administration of several drugs was planned to assess whether conditioned suppression will generalize out to other "panicogenic" drugs and provide a model for biological challenge paradigms in humans. Assessment of the effectiveness of anti-panic medications, (both acutely and chronically administered), to reduce the degree of conditioned suppression also was planned. Experiment 2 assesses whether a different drug, which does cross the blood-brain-barrier in rats and humans, could serve as a CS in a classical conditioning paradigm.

EXPERIMENT 1

Overview

The use of a drug as a conditioned stimulus (CS) in a classical conditioning paradigm has been accomplished several times (Cook, Davidson, Davis, & Kellerher, 1960; Turner & Altshuler, 1974; Turner, 1976; Vernon, 1966; Overton, Shen, & Tatham, 1993). The selection of epinephrine as the conditioned stimulus was based on several characteristics of the drug. Epinephrine produces various bodily sensations of arousal such as palpitations and increases in heart rate, respiration, and blood pressure (Gilman et al., 1990). These symptoms are similar to those postulated to function as conditioned stimuli in the interoceptive conditioning theory of panic disorder (Goldstien & Chambless, 1978). Cook et al. (1960) investigated whether various hormones could serve as conditioned stimuli in an avoidance paradigm, indicating that epinephrine (EPI) can serve as a CS in a classical conditioning paradigm. Epinephrine exhibits minimal crossover of the blood-brain-barrier (Weiner, 1985), which adds to the theoretical utility of epinephrine as a CS within the present project. The fact that EPI has no direct central mechanism minimizes the involvement of CNS neurotransmitter systems or structures implicated in biological models in the conditioned effects of the EPI. Therefore epinephrine possesses an ideal complex of stimulus properties to model the classical conditioning model of panic disorder.

Within the present experiment, rats received fifteen pairings of low dose epinephrine and inescapable shocks. The effects of administration of the same dose of epinephrine on a single lever food-reinforced response served as the index of a classically conditioned response (conditioned suppression). The purpose of this study is to assess whether peripheral autonomic arousal sensations could serve as a CS in a classical conditioned fear paradigm in which shock is the unconditionied stimulus (UCS), and whether biological challenge agents would generalize to the epinephrine cue.

Study Hypotheses

1) Epinephrine can acquire the ability to suppress operant behavior via multiple pairings with shock in the paired group.

2) Rats receiving unpaired presentations of epinephrine and shocks will not exhibit suppression of operant responding when tested.

3) Drugs that produce anxiety in panic patients more often than in healthy controls will generalize to the epinephrine CS, eliciting suppression as well.

4) Anti-panic drugs such as imipramine can produce anti-suppressive effects in the paired rats.

Methods

Subjects and Housing

Eight male Sprague-Dawley rats (325-371g) obtained from Taconic farm were housed in individual cages, and had free access to water at all times other than during experimental sessions. Prior studies demonstrating drug as CS effects each used male rats as subjects (Turner & Altshuler, 1976; Turner, 1976; Vernon, 1966; Overton, Shen, & Tatham, 1993). Sprague-Dawley rats were selected because the laboratory typically employed this strain and no strain differences in acquisition of drug as CS have been reported. Sample size per group (n=4) was similar to the size used in Turner and Altshuler's (1976) successful demonstration of amphetamine serving as a CS (n=5).

Free-feeding weight was determined following a three week period where rats were given 24 hour access to food. The rats were maintained at 85% of their free feeding weight to facilitate responding, with daily adjustment to the amount of chow (Harlan teklan Mouse/Rat Diet 7012) made based on the rat's current weight. Rats were food deprived for the 23 hours proceeding the sessions and fed standard rat chow immediately following experimental sessions. The amount of food given was adjusted each day to maintain the rats at 85% free feeding weight. The housing room was maintained on a 0700h lights-on, 1900h lights-off schedule, with all experimental sessions occurring during the light cycle. Housing rooms were maintained at 74^0 Fahrenheit and 50% relative humidity.

Apparatus

Operant and classical conditioning training occurred in the same chambers. The eight experimental chambers were standard operant chambers, with sound-attenuating, ventilating enclosures (Med-Associates). Chambers were equipped with two retractable response levers which had lamps mounted above them, a tone generator, a feedback relay, a food pellet dispenser, and a grid floor. Scrambled AC electric shocks produced by a constant current shocker could be delivered through the grid floor. Lighting was provided by a 5 watt overhead house light which was turned on at the beginning of all experimental sessions. Experimental events were recorded and controlled by MED-PC 2.0 running on an IBM PC located in an adjacent room.

Drugs

Drug solutions were prepared by mixing (-)-epinephrine bitartrate (Research Biochemicals Incorporated) in 0.9% saline solution (McGaw Inc.). Drug solutions were mixed fresh approximately every third session. The volume of injection was 1.0 ml/kg. A dose of 0.1 mg/kg was selected for training, which was based in part on Cook et al.'s (1960) use of epinephrine as a conditioned stimulus.

Procedure

Design. This experiment consisted of four phases. The parameters for classical conditioning and operant sessions were based in part on Turner and Altshuler (1976). In Phase 1, a period of training on a Variable Interval-60 second schedule of lever pressing was conducted. In Phase 2, repeated pairings of epinephrine and a train of shocks were administered. Phase 3 entailed a period of retraining on the operant response. Phase 4 consisted of CS only presentations in order to test for conditioned suppression. Table 1 presents the time-line for Experiment one.

Phase one-Training. All operant sessions were 30 minutes in duration and were conducted five days a week. Subjects received no drugs or shocks during this phase. All subjects were trained to press a single-lever for food reinforcement. All rats responded on the left lever (arbitrarily chosen), with the right lever being retracted during all sessions. The schedule of reinforcement was progressed from continuous reinforcement to a variable-interval 60-second schedule. The VI-60 second schedule remained the schedule of reinforcement throughout training and testing. Inter-reinforcement intervals for the VI-60 ranged between 0 and 120 seconds. Sixty training sessions on the VI-60 schedule were conducted prior to classical conditioning. Response rates for each minute, total response rate, and number of reinforcers earned were recorded.

Following the VI-60 training, all rats were given seven habituation sessions. These sessions involved placing the rats into the chambers with the levers retracted, and house lights on for 15 minutes before giving them an injection of normal saline. After the injection, rats were placed back into the chambers, for the same period of time that later conditioning and control sessions would require. These sessions were intended to habituate rats to the injection, and to introduce a 15-minute pre-injection period, as well as another 15-minute period that would later serve as a CS onset time during conditioning sessions. Several lines of evidence suggest that the context in which classical conditioning occurs may itself come to serve as a CS (Bouton & Bolles, 1979; Bouton, 1991; Landeira-Fernandez, 1996). The pre-injection period was included in an effort to reduce the potential role of context in later conditioning via latent inhibition.

Phase two: Classical Conditioning Trials. Following operant training, the subjects were randomly divided into two groups of four rats. Operant sessions were not conducted during this phase of the study. During this phase, rats were run on either conditioning or control sessions. A total of 15 classical conditioning sessions were conducted, randomly interspersed with 15 control sessions, one session being run each day.

On conditioning days rats received either saline or epinephrine injection 15 minutes after being placed into the chambers. As with habituation sessions, no levers were out, and the house lights were on during both the 15 minute pre-injection and post injection periods. Fifteen minutes after being injected, all rats were exposed to a series of inescapable shocks. Shocks were delivered with a 4.5 intershock interval, 0.5 second duration, and a 1.0 mA intensity. A total of 200 shocks were administered over a 16.7 minute period. Four rats experienced epinephrine before the onset of shock trains, and four received saline. To control for sensitization and pseudoconditioning, a modified Resclora (1967) procedure was implemented, in which the unpaired drug-shock group received injections of epinephrine at a randomly determined time between the hours of 0500-1900. During these random injections, the paired drug-shock group received injections of normal saline. These random-time injections were administered in an adjacent room and rats were placed into their home cages immediately following the injection.

The above procedure produced randomized presentations of epinephrine and shock for the unpaired group, and consistent pairings for the paired group. Table 2(a) outlines the presentation scheme for random and pre-session injections on conditioning days.

On control days, all rats received saline injections 15 minutes after being placed into the chambers. As with habituation sessions, no levers were out, and the house lights were on during both the 15-minute pre-injection and post-injection periods. During control sessions, no shocks were presented after the 15 minute "CS onset time," and the rats remained in the chambers for the exact amount of time as they did on conditioning days. Random-time injections were administered on control days, with all rats receiving saline. Table 2(b) presents the ordering for random and pre-session injections on control days.

Phase three: Retraining. Following the classical conditioning trials, all subjects were retrained on the VI-60 second schedule for 12 sessions. All rats received saline injections 15 minutes after being placed into the chambers. During both the 15-minute pre-injection and post-injection periods, no levers were out and the house lights were on. Operant sessions began at the end of the post-injection period. Response rates for each minute, total response rate, and number of reinforcers earned were recorded.

Phase four: Suppression Testing. On the initial testing day, all rats were then placed into the chambers, and after 15 minutes received a 0.1mg/kg injection of epinephrine. During both the 15-minute pre-injection and post-injection periods, no levers were out, and the house lights were on. At the end of the post-injection period, operant session began. Response rates for each minute, total response rate, and number of reinforcers earned were recorded. Subsequent testing trials were conducted with 0.17mg/kg and 0.3mg/kg dosages, separated by two days of operant sessions without drug administration.

Data Analysis. Assessment of conditioned suppression to the epinephrine CS was conducted with the Mann-Whitney U test. The Mann-Whitney U test is a powerful non-parametric statistic which is suitable as an alternative to the t-test, especially when sample sizes are small (Siegel, 1956). The groups were compared in terms of percentage change in mean response rates from the last four sessions during retraining to testing sessions. Overall session response rates changes, as well as changes in each of the first 5 minutes of the sessions, were examined.

Results

Figure 4 presents group means for the change from baseline responding across the three dosages tested. The average of the last three retraining sessions was used to compute the baseline. Contrary to prediction, subjects in the unpaired group showed greater suppression to the epinephrine CS than the paired group, at the 0.1mg/kg dose (Mann-Whitney U = 0, $p<.05$). No significant differences were found between the groups at either the 0.17 mg/kg (Mann-Whitney U = 7, n.s.) or 0.3 mg/kg doses (Mann-Whitney U = 6, n.s.).

Figure 5 presents the individual subject's change from baseline response rates for paired (panel a) and unpaired (panel b) subjects. While generally showing less suppression to the epinephrine, the paired subjects did show greater homogeneity in response to the varying drug doses that did the unpaired subjects.

The first five minutes of the test sessions also were analyzed. Responding during the 5 five minutes of the testing sessions was compared to the average response rates during minutes 1-5 of the last three retraining sessions. Figure 6 presents the group means for minutes 1 through 5 of the 0.1 mg/kg (panel a), 0.17 mg/kg (panel b), and 0.3 mg/kg (panel c). The group means for the 0.1 mg/kg test were significantly different during the fifth minute (Mann-Whitney U = 0, $p< .05$) but not during minutes 1-4. During the first 5 minutes of the 0.17 mg/kg test session, a significant difference was found only during the third minute (Mann-Whitney U = 0, $p< .05$), with the unpaired rats demonstrating greater suppression. There were no significant differences between the two groups during the first five minutes of the 0.3 mg/kg test session.

Discussion of Experiment 1

Experiment 1 failed to confirm hypotheses one and two. Because conditioning to the epinephrine CS did not occur, the planned generalization tests could not be undertaken. Likewise, no anti-panic drugs were administered to attenuate suppression of responding.

Several reasons for the failure of the epinephrine CS to suppress responding despite multiple pairings with shock are possible. A few explanations for the lack of conditioning to the drug CS are pharmacological. Epinephrine was administered ip in this experiment, whereas in the one published demonstration of epinephrine functioning as a CS, the epinephrine was administered iv (Cook et al., 1960). It is unclear exactly why the epinephrine administered ip would act differently with a different route; however, two plausible explanations can be offered. Epinephrine administered iv has essentially 100% bioavailability and rapid onset, whereas ip or im injections have a more variable bioavailability and slower onset time. The fact that epinephrine acts as a local vasoconstrictor also could cause some variability in onset time as well as bioavailability. Variability in drug onset or duration would be expected to degrade the salience of the drug CS.

Another possible reason for the failure of conditioning to the CS that is also related to the pharmacology of epinephrine is the fact that stressors cause the release of endogenous epinephrine (Ferreira, Gollub, & Vane, 1969). If all subjects experienced the release of endogenous epinephrine from the stress of injections, then this would be expected to degrade the contingency between epinephrine and shocks. All rats received two injections per day during conditioning phase and one per day throughout the rest of the experiment. Therefore, there were numerous occasions in which epinephrine (endogenous) would have been paired with shocks for both groups and not followed with shocks for both groups. For paired rats, the endogenous release of epinephrine when not followed by shocks would act as extinction trials and, for unpaired rats, endogenous release prior to shocks would function as conditioning trials. While this is an interesting possibility, the contribution of this factor, if any, is probably small because the paired rats were likely able to discriminate between low levels of endogenous epinephrine and the ip injection levels.

Additional possible explanations for the lack of conditioning involve methodological shortcomings. Despite the sound attenuating enclosures to the chambers, it is plausible that subjects were able to detect sounds from adjacent boxes. Because all rats were run on the same type of session each day (i.e., all on control or all on conditioning), any detectable sounds from adjacent chambers would represent a serious methodological confound. With the exception of the subject in box 1, every subject might have been exposed to several minutes of either silence (control sessions) or noises such as vocalizations (conditioning sessions) prior to the beginning of its session. Based on the overshadowing effect (Pavlov, 1927), one would predict that if vocalizations were audible, they would be more salient that the drug cue. If animals were able to detect vocalizations, then these cues would precede each shock session with 100% accuracy in prediction. Coupled with the hypothesized variability in the onset and degradation of the epinephrine CS, one could speculate that the drug CS provided no information over and above what the audio cues were consistently providing. A large body of literature suggests that conditioning to an uninformative CS will be blocked in the presence of a more reliable predictor (Kamin, 1968, 1969).

The use of a fixed intershock interval presents an additional possible source of predictability for subjects. Because shocks occurred at regular intervals, the rats from both groups were probably exposed to several shocks in the presence of endogenously released epinephrine.

EXPERIMENT 2

Overview

Experiment 1 failed to demonstrate the predicted conditioned association between epinephrine and shock presentations. Attempts were made to eliminate or minimize each of the possible reasons for the failure of conditioning in Experiment 1. The drug used for the CS was changed from epinephrine to yohimbine. Yohimbine, a potent panicogen, readily crosses the blood brain barrier and has a well-accepted mechanism for its anxiogenic properties (antagonism of the α_2 -adrenergic autoreceptor). Unlike epinephrine, yohimbine does not cause local vasoconstriction, which may have contributed to the lack of conditioning in Experiment 1. Additionally, yohimbine was chosen because it is not a hormone; and, therefore, the possibility of endogenous release during the stress of injections/handling was eliminated.

The design of the experiment was significantly modified to minimize transmission of auditory cues that might overshadow the drug CS. Several manipulations, structural and procedural, were used to reduce cues from adjacent boxes. Procedurally, equal numbers of subjects were run on control and conditioning sessions on the same day. Control sessions now consisted of VI-60 second operant sessions. Two structural changes to the apparatus were implemented: the addition of white noise and additional sound attenuating insulation. The purpose of this study is to evaluate yohimbine as a CS and to eliminate many of the possible confounds from Experiment 1.

Hypotheses

1) Yohimbine can acquire the ability to suppress operant behavior via multiple pairings with shock.

2) Rats receiving unpaired presentations of yohimbine and shocks will not exhibit suppression of operant responding when tested.

3) Drugs which produce anxiety in panic patients more often than in healthy controls will generalize to the yohimbine CS, eliciting suppression as well.

4) Anti-panic drugs such as imipramine can produce anti-suppressive effects in the paired rats.

Methods

Subjects and Housing

The eight male rats from Experiment 1 also served as subjects for Experiment 2. Although no definite conditioning to the epinephrine CS had been demonstrated, it remained possible that prior group assignment could influence further conditioning. It was, therefore, decided to randomize prior group allocation across the two groups in the present experiment. Table 4 (a) and Table 4 (b) show group allocation for Experiment 1 and 2, respectively. As shown in the tables, two rats from the former paired group were placed into the unpaired group, and vice versa for the unpaired group. Housing and feeding conditions were identical to those described in Experiment 1. Again, sample size per group (n=4) was similar to the size used in Turner and Altshuler's (1976) successful demonstration of amphetamine serving as a CS (n=5).

Apparatus

The experimental chambers from Experiment 1 were modified for Experiment 2. A Gerbrands masking noise generator was installed with white noise being sent to speakers located inside the enclosure of each chamber. To reduce the possibility of animals receiving auditory cues from adjacent chambers, 1.5-cm thick industrial grade Styrofoam (Duramate, Dow Chemical

Company. Midland, MI) was installed. The insulation was mounted tightly to all exterior surfaces of the enclosures, including the enclosure doors and the enclosure bottoms. The addition of the insulation noticeably decreased noises (e.g., relay clicks, vocalizations during shocks) that were audible from outside the chambers.

Drugs

Drug solutions were prepared by mixing yohimbine hydrochloride (Research Biochemicals Incorporated) in 0.9% saline solution (McGaw Inc.). Drug solutions were mixed fresh every day. Based on a literature search and pilot data, a training dose of 1.0 mg/kg was selected (Dwoskin, Neil, & Sparber, 1988; Browne, 1981; Katz, 1984).

Procedure

Design. This experiment consisted of four phases. In Phase 1, a dose-response curve for yohimbine was determined. Phase 2 involved classical conditioning trials. Phase 3 entailed a brief period of retraining on the operant response. Phase 4 consisted of CS only presentations in order to test for conditioned suppression. Table 3 presents the time line for Experiment 2.

Phase one: Dose-response curve determination. All operant sessions were 30 minutes in duration, and were conducted five days a week. Based on a literature search, the onset time for yohimbine at this dosage was determined to be 30 minutes, and, therefore the CS onset time was extended from the 15-minute period used in Experiment 1 to 30 minutes (Dwoskin, Neil, & Sparber, 1988; Browne, 1981; Katz, 1984).

Following a period of nine days during which rats were run on a VI-60 second schedule, a dose-response curve for yohimbine was determined. During two separate sessions, each rat received a dose of yohimbine before the beginning of an operant session. A range of dosages (0.56- 5.6 mg/kg) was tested, with rats receiving a different dose before each session. Individual rats received different dosages on different days. Two daily sessions of VI-60 operant responding separated the drug administration sessions.

Figure 7 displays the dose-response relationship between yohimbine and operant responding. Visual inspection of the dose-response curve indicated a clear increase in responding occurred at the dosage of 1.0 mg/kg. The training dose for conditioning was selected as 1.0 mg/kg, because the unconditioned effects of the drug are in the opposing direction of the dependent variable (e.g., enhancement of responding verses suppression).

Phase two: Classical Conditioning Trials. The eight subjects were divided into two equal groups of four rats as described under the Subjects section. Classical conditioning trials were similar to those used in Experiment 1, with several exceptions. The CS drug employed for training was yohimbine (1.0 mg/kg). With the exception of the inter-shock-interval (ISI), the parameters for the shocks were unchanged. In order to decrease the predictability of shock occurrence, the ISI was changed from a fixed 4.5-second schedule to a variable schedule with a mean of 4.5 seconds. In this experiment, control sessions were changed to operant sessions, instead of periods during which the rats simply remained in the chambers without responding.

Rats were run for eight conditioning sessions, and eight control sessions, one session per day. To minimize any possible predictability of audio cues, both conditioning and control sessions were given randomly during the same day. The randomization pattern used is depicted in Table 5. For each trial, four of the eight rats experienced a conditioning session, and the other four experienced a control session. Trials began on row A, and went through D, then repeated this sequence throughout training

(ABCDABCD...), one trial per day. Each rat received a total of eight conditioning and eight control trials, with no correlation between the type of session it received and the session type rats in adjacent chambers received. A few rats failed to respond at all on control trials, therefore jeopardizing the ability to collect adequate pre-test baselines and data during test sessions. Because of this extreme suppression evident in many subjects' response rates during control trials, an unplanned period of six operant retraining sessions was introduced between trial 9 and 10.

The same injection randomization procedure used in Experiment 1 was again implemented to control for sensitization and pseudoconditioning. Pseudoconditioning refers to the generation of a response that appears to be a conditioned response, but is not a result of conditioning (Rachlin, 1991). Unpaired rats received yohimbine 1.0 mg/kg at randomized times between the hours of 0500-1900 on days where they underwent conditioning sessions and received saline before conditioning sessions. Paired rats received saline injections during randomized injections and yohimbine (1.0 mg/kg) before their conditioning sessions. On control sessions, both unpaired and paired rats received injections of normal saline before their VI-60 session and at randomly determined times. These random-time injections were administered in an adjacent room and rats were placed into their home cages immediately following the injection.

The above procedure randomized presentations of yohimbine and shock for the unpaired group and provided consistent pairings for the paired group. Table 6 (a) presents the scheme for random and pre-session injections for rats undergoing conditioning sessions. The scheme for control session injections is presented in Table 6(b). Pre and post-injection periods were identical to those in Experiment 1 (e.g., levers retracted, house lights on) except for the 30-minute post injection period.

On days where a rat underwent a conditioning session, it was exposed to a series of inescapable shocks thirty minutes after being injected with either saline of yohimbine. On days where a rat underwent a control session, it was allowed to work for food on a VI-60 second schedule which began 30 minutes after the saline injection.

Phase three: Retraining. Following the classical conditioning trials, all subjects were retrained on the VI-60 second schedule for 8 sessions. All animals received saline injections 15 minutes after being placed in the chambers, and had the same 30-minute wait until the operant session began. Response rates for each minute, total response rate, and number of reinforcers earned were recorded.

Phase four: Suppression Testing. On the initial testing day, all rats received a 1.0 mg/kg injection of yohimbine after being in the chambers for 15 minutes. After 30 minutes elapsed, the operant sessions began. Response rates for each minute, total response rate, and number of reinforcers earned were recorded. An additional testing trial was conducted with 3.0 mg/kg, separated by 2 days of operant sessions without drug administration.

Data Analysis. Assessment of conditioned suppression to the yohimbine CS was conducted using the Mann-Whitney U test. The Mann-Whitney U test is a powerful non-parametric statistic which is suitable as an alternative to the t-test, especially when sample sizes are small (Siegel, 1956). The groups were compared in terms of percentage change in response rate from the last four sessions during retraining to testing sessions. Overall session response rate changes as well as changes during the first 5 minutes of the sessions were examined.

Results

Response rates for two rats (one from each group) failed to recover during the retraining phase and their data were excluded from analysis. Figure 8 presents group means for the change from baseline responding across the two doses tested. The average of the last three retraining sessions was used to compute the baseline. Contrary to prediction, subjects in the unpaired group generally showed greater suppression to the yohimbine CS than the paired group. The two groups were not significantly different at either the 1.0 mg/kg (Mann-Whitney U = 0, n.s.) or 3.0 mg/kg (Mann-Whitney U = 3, n.s.) doses. Figure 9 presents the individual subject's change from baseline response rates for paired (panel a) and unpaired (panel b) subjects. Of the remaining six rats, some displaying markedly reduced responding (making no responses until 3-4 minutes elapsed) during the first several minutes of the baseline sessions. Because rats with low baseline response rates would have to be excluded, analysis of the first five minutes of the test sessions could not be undertaken.

Discussion of Experiment 2

Experiment 2 failed to confirm hypothesis one or two. Despite controlling for many factors that were believed to have prevented associative conditioning to the drug CS in Experiment 1, the yohimbine CS did not suppress responding in the predicted direction. Because no conditioned suppression was demonstrated to the drug CS, hypotheses three and four could not be tested.

A possible explanation for the failure of yohimbine to suppress responding in the paired rats is the behavioral history of these subjects. In Experiment 1, it was strongly suspected that subjects were attending to exteroceptive (auditory) cues coming from adjacent boxes. If this is indeed what occurred, then interference with further training is highly possible. It may be that the rats were inadvertently trained to attend to a audio cues during Experiment 1, and Experiment 2 did not adequately facilitate subjects' to attending to the drug cue.

Data from the subjects' performance during the classical conditioning phase is consistent with this hypothesis. After nine of the 16 planned trials, the rats were given impromptu retraining on the VI-60 schedule. This retraining period was undertaken because response rates on control (VI-60) sessions were extremely suppressed for several rats. Watching the rat's behavior on control days, it became apparent that despite the addition of the masking noise and the insulation, rats were still able to detect audio cues. Many rats responded inconsistently during their VI-60 sessions, responding very little on trials where a rat in an adjacent box received shocks, and closer to baseline on days where rats in adjacent boxes were also on a VI-60 session. A striking example of this effect is diagrammed in Figure 11. This rat's minute-by-minute response rates for four control sessions (e.g., VI-60) are plotted together. On two of the days plotted, the subject in the adjacent box is receiving shocks, and on the other two, the adjacent box is undergoing a control (VI-60) session. As can be seen, the subject clearly reacts differently during days when the subject located above him is receiving shocks (open circles in the Figure). On adjacent-VI-60 days (closed diamonds), this subject's responses are not suppressed, with the exception of the first several minutes. It should be noted that on the two adjacent-shocked sessions, this subject's response rate begins to recover after about 17 minutes into the session. This time is noteworthy in that is corresponds to the termination of shocks in the adjacent chamber, supporting the suspicion that the rats were attending to exteroceptive stimuli from adjacent boxes, in the form of vocalizations. It seems likely that the subjects were making discriminations about the likelihood of shock (demonstrated in suppression) based on the exteroceptive stimuli instead of the intended drug stimuli.

GENERAL DISCUSSION

Two attempts were undertaken to model the interoceptive conditioning theory of panic disorder in Sprague-Dawley rats. In Experiment 1, classical conditioning to the stimulus effects of epinephrine did not occur, and several several possible explanations for this failure to demonstrate conditioning were discussed. Finding that the unpaired rats showed greater suppression to the epinephrine than the paired group was unexpected. While many of the reasons detailed in the discussion of Experiment 1 might explain why no conditioned association to the epinephrine was demonstrated in the paired rats, they do not address the paradoxical suppression shown by unpaired rats. Findings from the CS "reinstatement" procedure utilized by Haroutunian, Riccio and others (Haroutunian & Riccio, 1977; Spear, 1973) might be used to suggest a possible reason for thé unpaired rat's suppression in Experiment 1. Haroutunian and Riccio (1977) proposed that epinephrine, when administered in the presence of contextual cues previously associated with shocks, produce arousal and provide additional sources of "memory attributes" as a reminder of the previously learned relationship. Essentially, it has been argued that a hormone such as epinephrine (Haroutunian & Riccio, 1977) or ACTH (Haroutunian & Riccio, 1979) can act as an internal cue which reactivates a memory of the aversive conditioning. This hormonally-induced state must be experienced in the presence of the contextual cues associated with shocks in order for the reinstatement effect to be demonstrated (Haroutunian & Riccio, 1977).

One might assume that some conditioning to the contextual stimuli in the present experiment occurred in both groups of rats. This assumption is partially substantiated by the gradual recovery of responding across the twelve retraining sessions. With regard to contextual conditioning, these retraining sessions can be considered extinction trials, serving to degrade the context + shock association. The unpaired rats in this experiment received their injections of epinephrine in their home cages and had never experienced the epinephrine in the presence of the chambers. It is possible that the exogenous epinephrine mimicked the internal state these rats experienced during the conditioning trials. This internal state in the presence of the previously feared context may have served as a "reminder." In the same vein, but more conservatively stated, the epinephrine may have created an additional discriminative stimulus (internal) that signaled the possible onset of shock. Contrary to the unpaired rats, the rats in the paired group experienced the exogenous epinephrine before each of the fifteen conditioning sessions, allowing the development of habituation to any contextual and hormonal enhancement effect.

Another interpretation of the data that can possibly explain the greater suppression in unpaired rats' responding compared to the paired rats involves tolerance to epinephrine. According to this interpretation, the unpaired rats' suppression of responding would be a result of the unconditioned effects of epinephrine. A large body of literature suggests that the development of tolerance is context-dependent (Siegel, 1975; Siegel, Hinson, Krank, & McCully, 1982; MacRae, Scoles, & Siegel, 1987). The unpaired rats did not experience exogenous epinephrine in the test chambers until the test sessions, instead receiving the epinephrine in their home cage context. The paired rats, however, received all fifteen epinephrine injections in the experimental chamber context. As the training dose of epinephrine produces response suppression as an unconditioned effect, the paired rats may have developed a context-specific tolerance to its effects while the paired rats did not. This potential confound, coupled with a lack of conditioning to the epinephrine drug stimulus, could have resulted in the unpaired group demonstrating greater suppression than the paired group. It should be noted that the possible interpretations listed above are not mutually exclusive. Indeed, it is quite possible that several of these factors (e.g., tolerance, bioavailibity problems, endogenous release of epinephrine) were involved.

Using a drug as a CS in a classical conditioning paradigm is a difficult undertaking (Revusky, Davey, & Reilly, 1987). Often many doses must be piloted because some drugs are able to function as CS's only within a narrow range of doses (Bormann & Overton, 1990). Because this project involved only one small group of rats, testing across a full range of doses to determine what doses, if any, could function as a CS obviously could not undertaken. Further experiments were not undertaken because of the time involved and budgetary reasons. It remains possible that a different dose or route of administration such as intravenous infusion can produce conditioned suppression to epinephrine. If other panicogenic drugs produce a conditioned response in animals trained with epinephrine as a CS, this outcome would obviously be consistent with the interoceptive conditioning theory of panic disorder onset.

The present study included many limitations. The failure to demonstrate conditioned suppression may have resulted from many factors which have already been discussed. Because of these limitations, the interoceptive conditioning model of panic disorder is neither supported nor refuted by the findings. Although the unpaired rats paradoxically exhibited greater suppression when administered epinephrine, this outcome cannot be taken as evidence against the interoceptive conditioning model of panic disorder. Numerous alternative hypotheses besides an inadequacy in the interoceptive conditioning model (most notably context-dependent tolerance in the paired rats) might explain the failure to demonstrate conditioned suppression.

TABLES

Table 1. Timeline for Experiment One

Phase One-Operant Conditioning	Sixty sessions-VI-60 second schedule
Phase Two-Classical Conditioning	Thirty sessions-randomly presented • Fifteen conditioning • Fifteen control
Phase Three-Retraining	Twelve sessions
Phase Four-Testing	Doses tested: • 0.1 mg/kg-one session • 0.3 mg/kg-one session • 0.17 mg/kg-one session * each test session was proceeded by at least two drug-free operant sessions.

Table 2 (a). Injection routine for conditioning days.

Group	Pre-Session Injection	Random Injection
Paired n=4	Epinephrine	Saline
Unpaired n=4	Saline	Epinephrine

Table 2 (b). Injection routine for control days.

Group	Pre-Session Injection	Random Injection
Paired n=4	Saline	Saline
Unpaired n=4	Saline	Saline

Table 3. Timeline for Experiment Two.

Phase One- Dose Response Curve for Yohimbine	Thirteen sessions • Nine regular VI-60 sessions • One session with each rat receiving a dose of yohimbine between 0.56-5.6. • Two regular VI-60 sessions. • One session with each rat receiving a dose of yohimbine between 0.56-5.6.
Phase Two-Retraining	Two regular VI-60 sessions
Phase Three -Classical Conditioning	Sixteen sessions-(half the subjects received conditioning and half received control sessions each day) • Eight classical conditioning sessions • Eight control sessions *(An unplanned period of 6 retraining sessions had to be introduced between sessions 9 and 10).
Phase Three-Retraining	Eight sessions
Phase Four-Testing	Doses tested: • 1.0 mg/kg-one session • 3.0 mg/kg-one session * each test session was proceeded by at least two drug-free operant sessions.

Table 4 (a). Group allocation for Experiment 1.

Box	Status	Box	Status	Box	Status	Box	Status
1	Unpaired	3	Paired	5	Paired	7	Unpaired
2	Unpaired	4	Paired	6	Paired	8	Unpaired

Table 4 (b). Group allocation for Experiment 2.

Box	Status	Box	Status	Box	Status	Box	Status
1	Unpaired	3	Paired	5	Unpaired	7	Paired
2	Paired	4	Unpaired	6	Paired	8	Unpaired

Table 5. Randomization Table for experiment two.

TRIAL	**BOX**			
A	▨ 1	▨ 3	5	7
	2	4	▨ 6	▨ 8
B	1	▨ 3	5	▨ 7
	2	▨ 4	6	▨ 8
C	1	3	▨ 5	▨ 7
	▨ 2	▨ 4	6	8
D	▨ 1	3	▨ 5	7
	▨ 2	4	▨ 6	8

Table 6 (a). Injection routine for conditioning days, Experiment 2.

Group	Pre-Session Injection	Random Injection
Paired n=4	Yohimbine	Saline
Unpaired n=4	Saline	Yohimbine

Table 6 (b). Injection routine for control days, Experiment 2.

Group	Pre-Session Injection	Random Injection
Paired n=4	Saline	Saline
Unpaired n=4	Saline	Saline

FIGURES

Figure 1. Panic rates for panic disorder patients and healthy controls following different doses of CCK-4

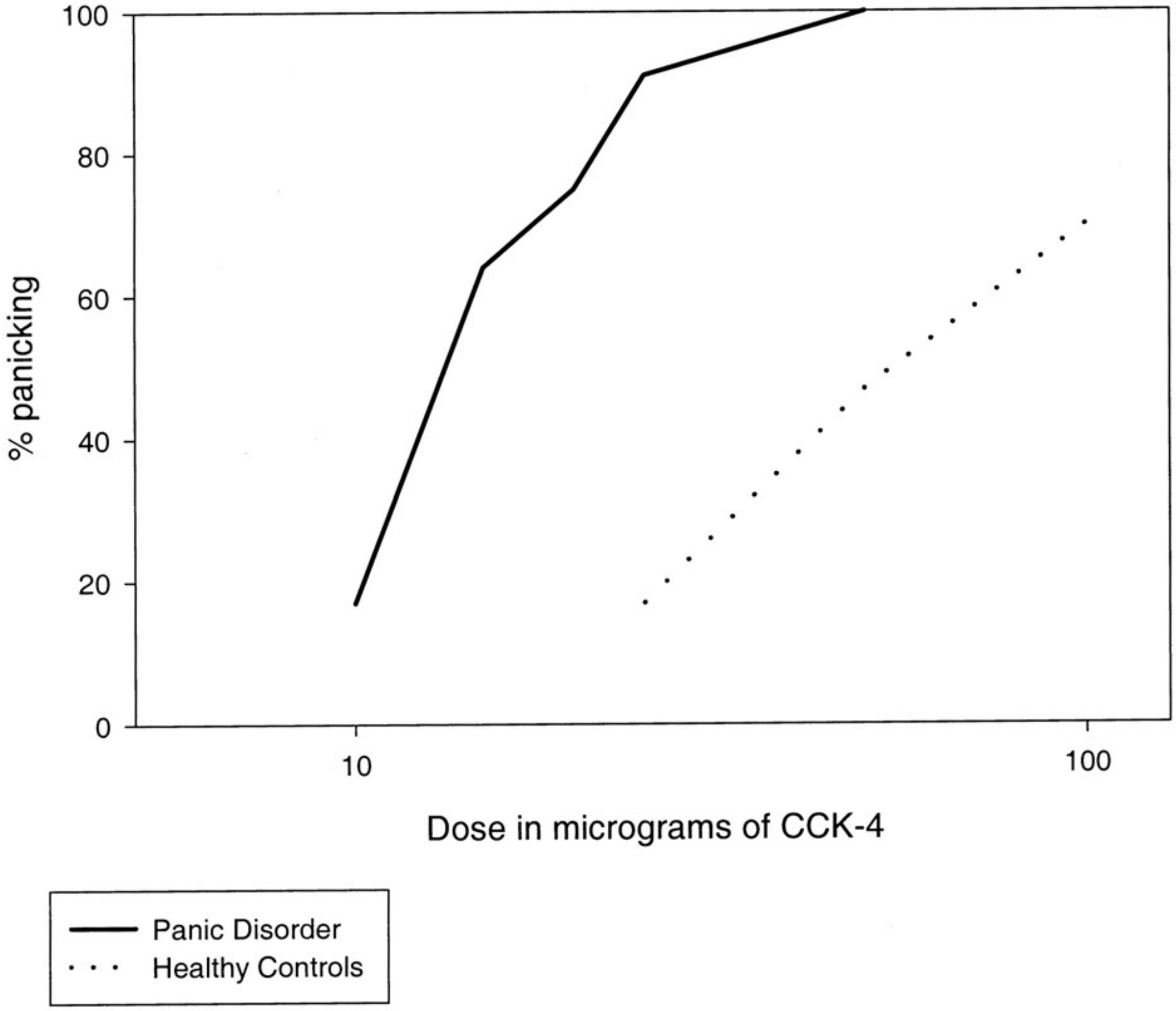


Figure 2: A cognitive model of panic attacks. Adapted from Clark (1986).

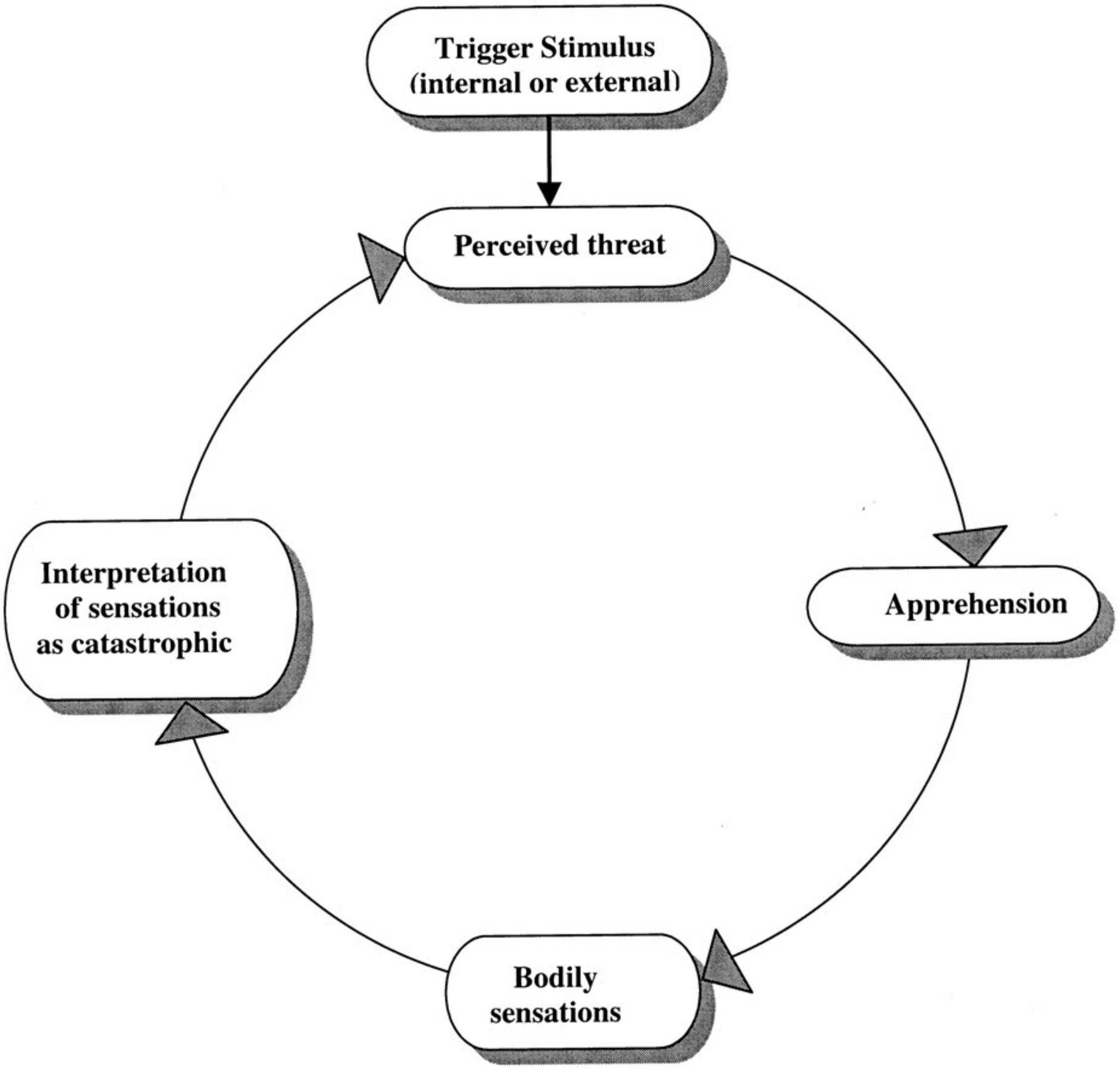

Trigger Stimulus
(internal or external)
Perceived threat
Apprehension
Bodily sensations
Interpretation of sensations as catastrophic

Figure 3: Classical Conditioning model for panic disorder.

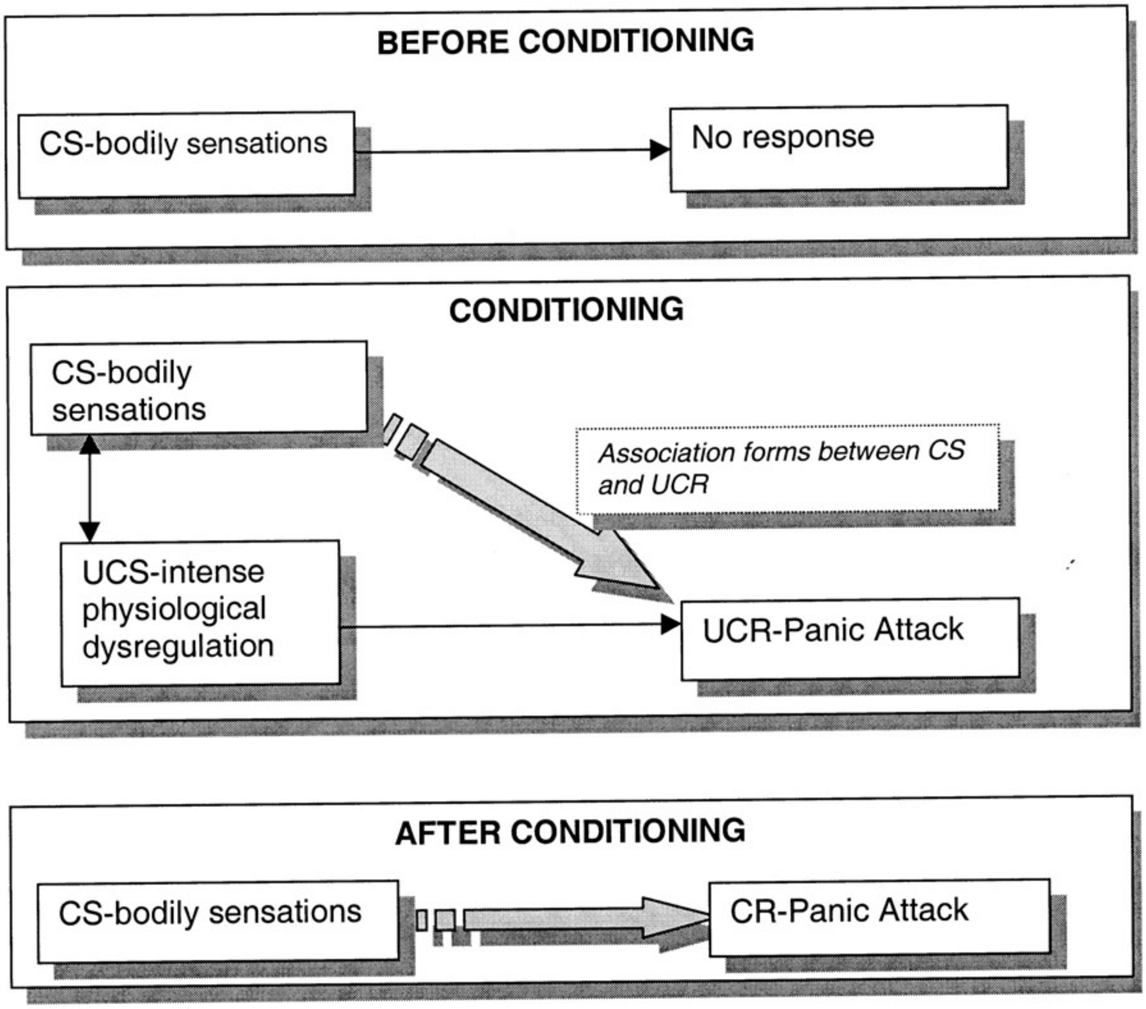

BEFORE CONDITIONING
CS-bodily sensations
No response
CONDITIONING
CS-bodily sensations
Association forms between CS and UCR
UCS-intense physiological dysregulation
UCR-Panic Attack
AFTER CONDITIONING
CS-bodily sensations
CR-Panic Attack

Figure 4: The Learned Alarm model for the development of panic disorder.
Adapted from Barlow (1988).

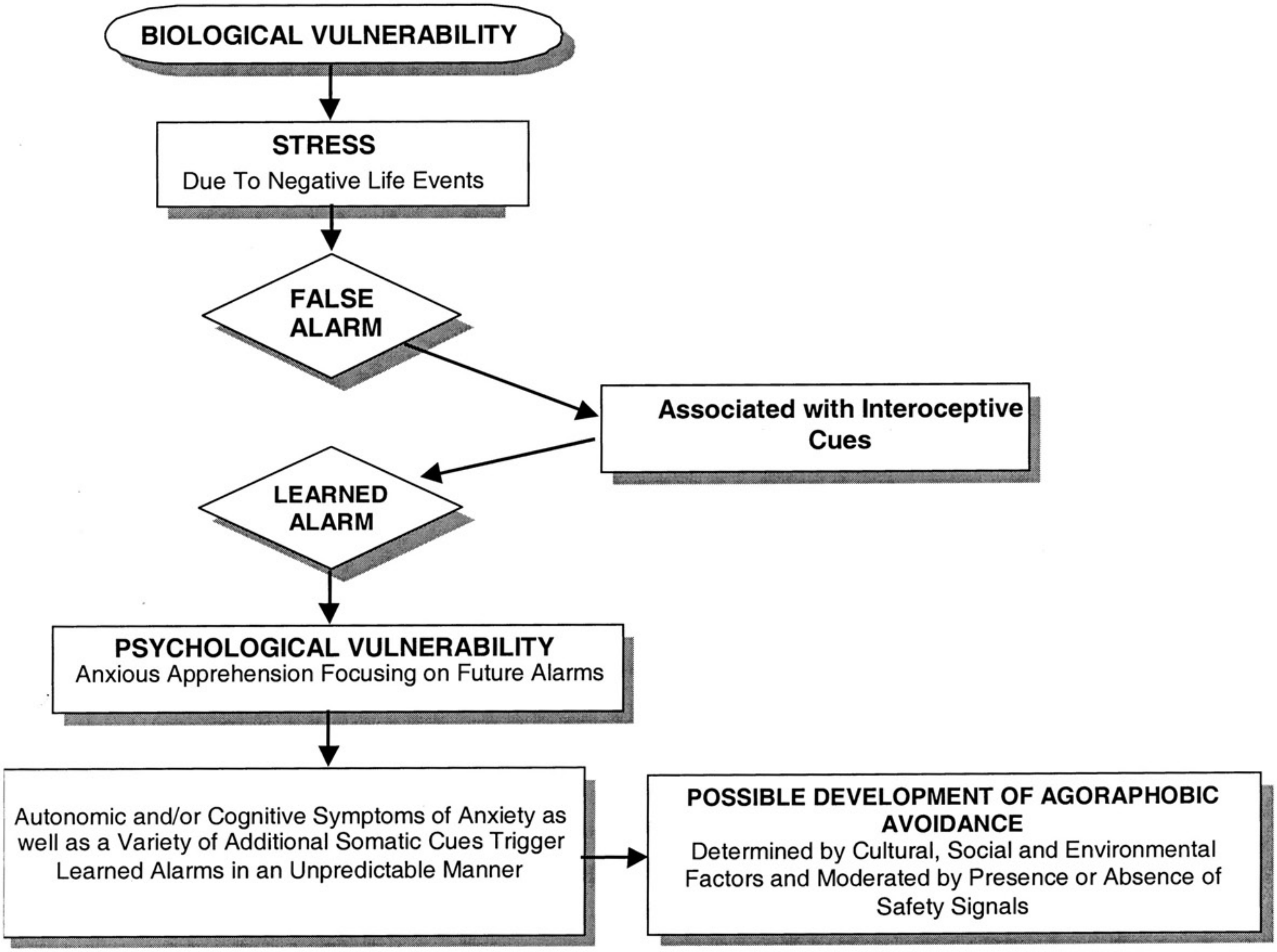

BIOLOGICAL VULNERABILITY
STRESS
Due To Negative Life Events
FALSE ALARM
Associated with Interoceptive Cues
LEARNED ALARM
PSYCHOLOGICAL VULNERABILITY
Anxious Apprehension Focusing on Future Alarms
Autonomic and/or Cognitive Symptoms of Anxiety as well as a Variety of Additional Somatic Cues Trigger Learned Alarms in an Unpredictable Manner
POSSIBLE DEVELOPMENT OF AGORAPHOBIC AVOIDANCE
Determined by Cultural, Social and Environmental Factors and Moderated by Presence or Absence of Safety Signals

Figure 5: Group mean suppression across three doses of epinephrine.

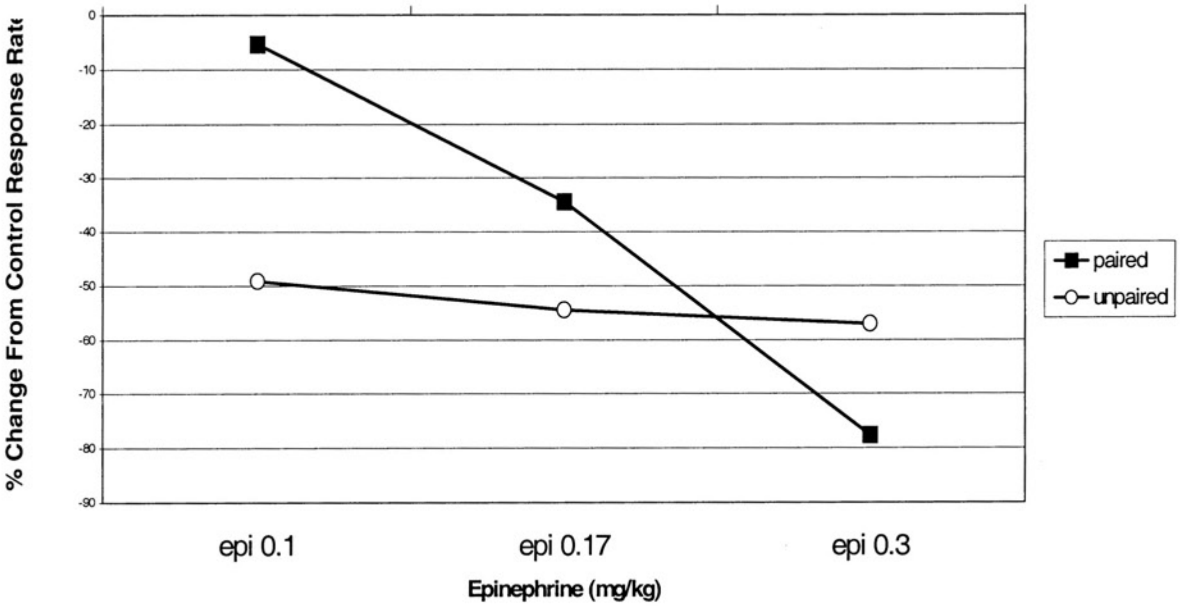


Figure 6a: Individual Paired rats suppression across doses tested.

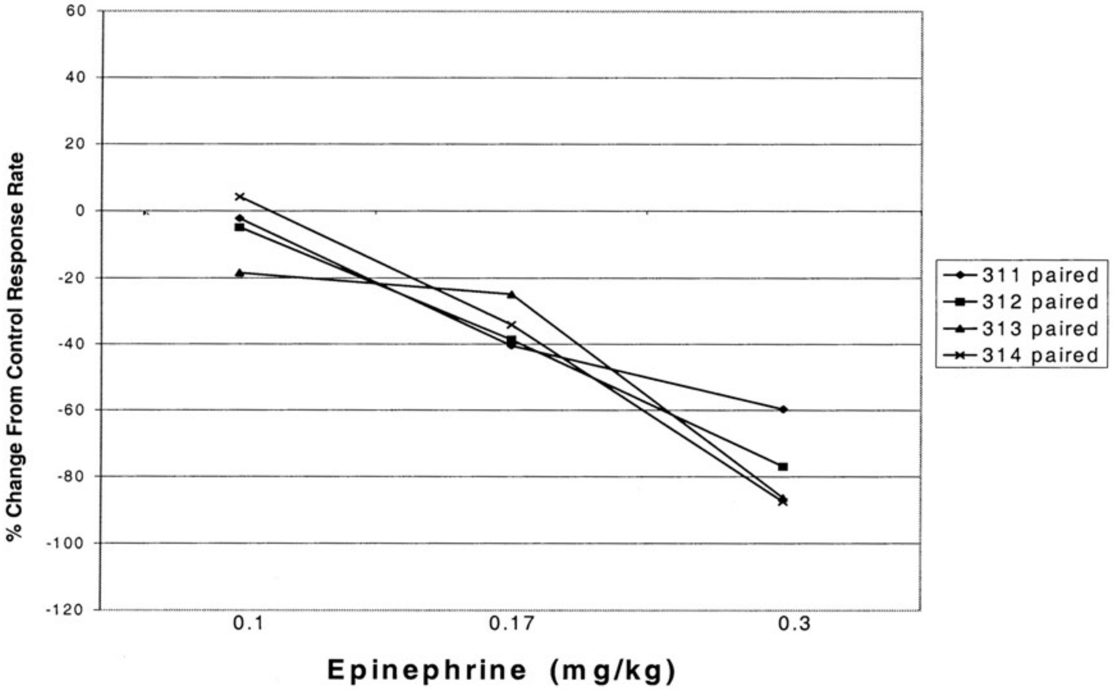


Figure 6b: Individual Unpaired rats suppression across doses tested.

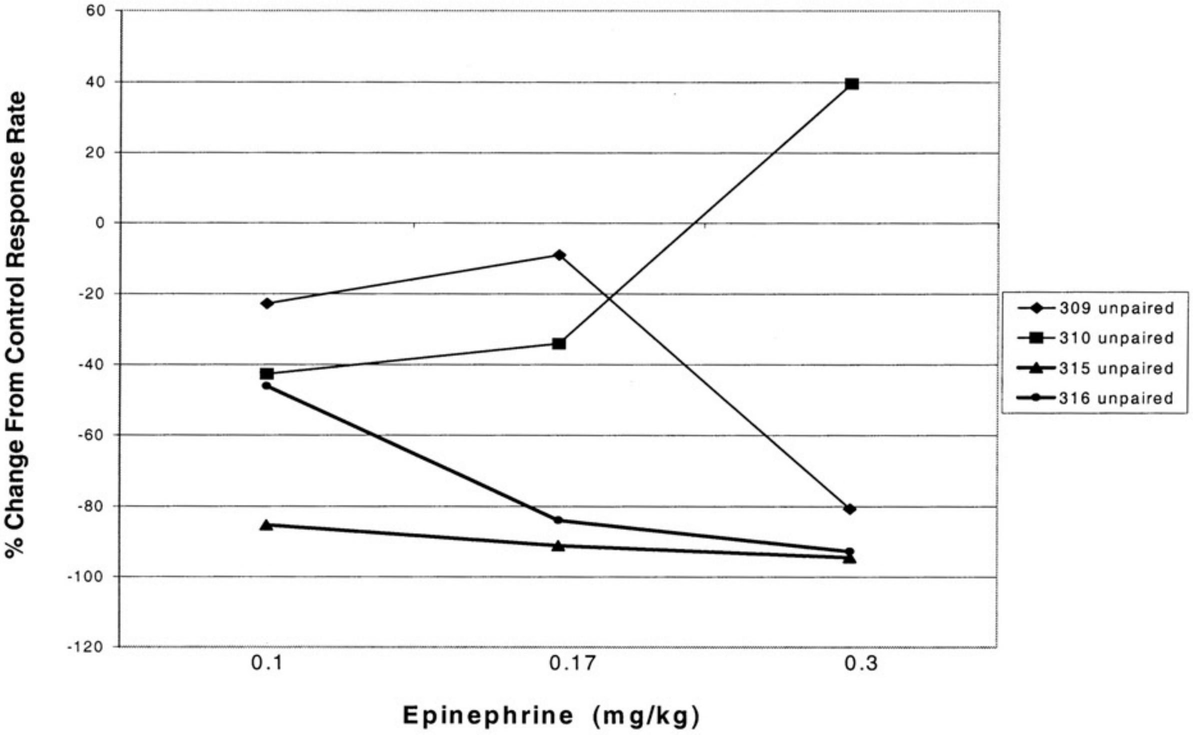


Figure 7a: Mean group suppression during minutes 1-5, 0.1 mg/kg epinephrine

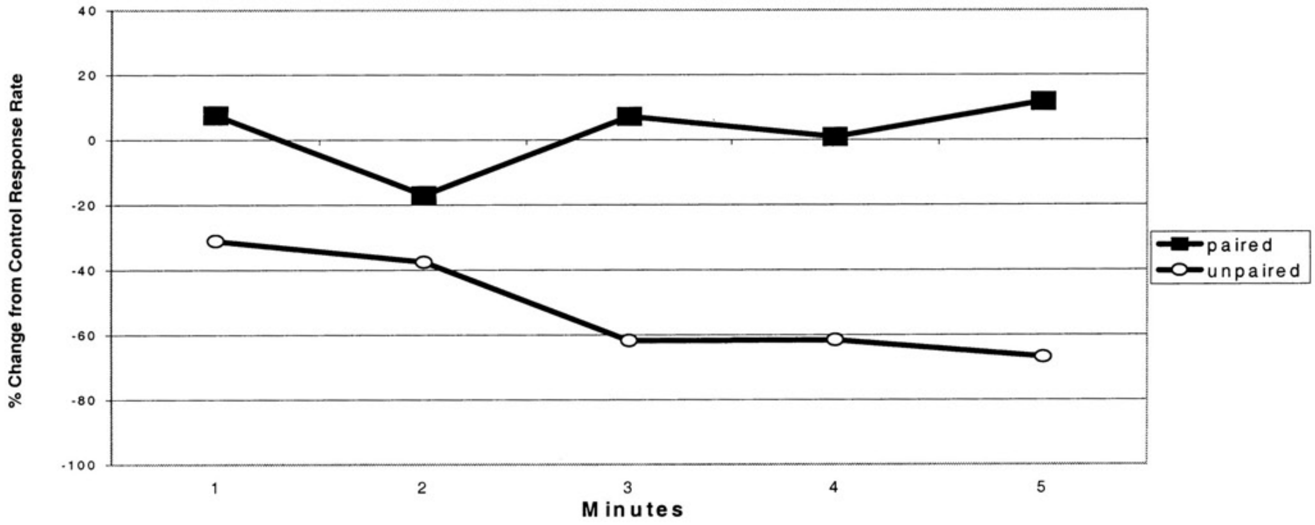


Figure 7b: Mean group suppression during minutes 1-5, 0.17 mg/kg epinephrine

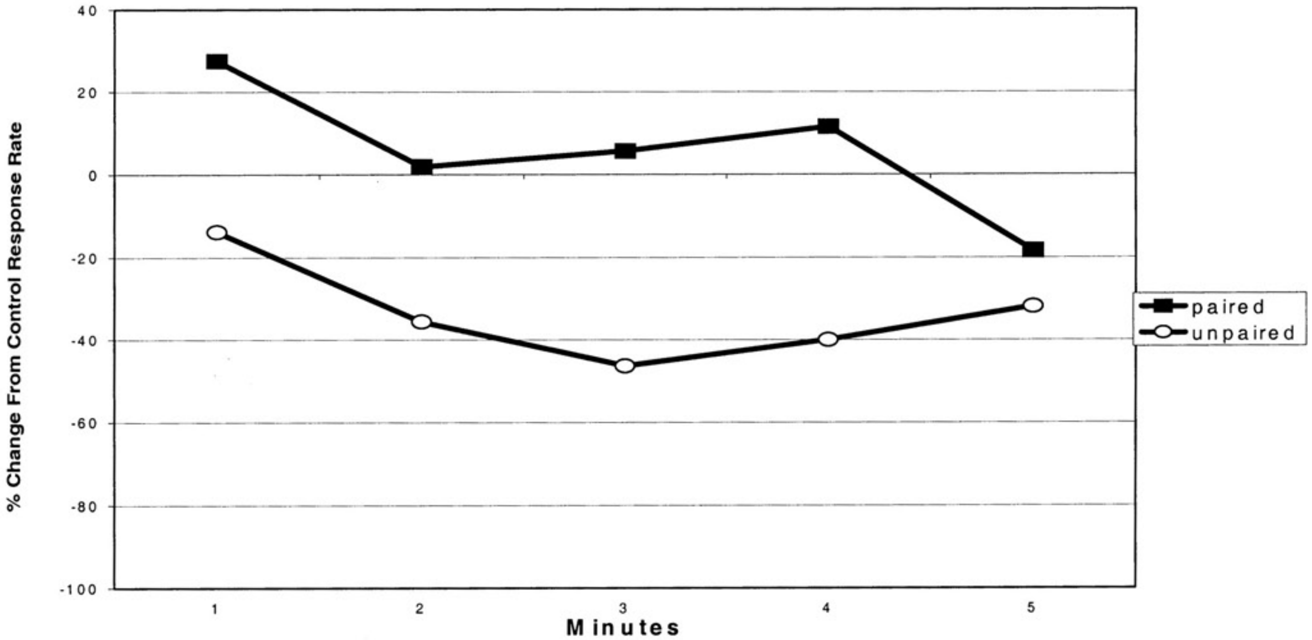


Figure 7c: Mean group suppression during minutes 1-5, 0.3 mg/kg epinephrine

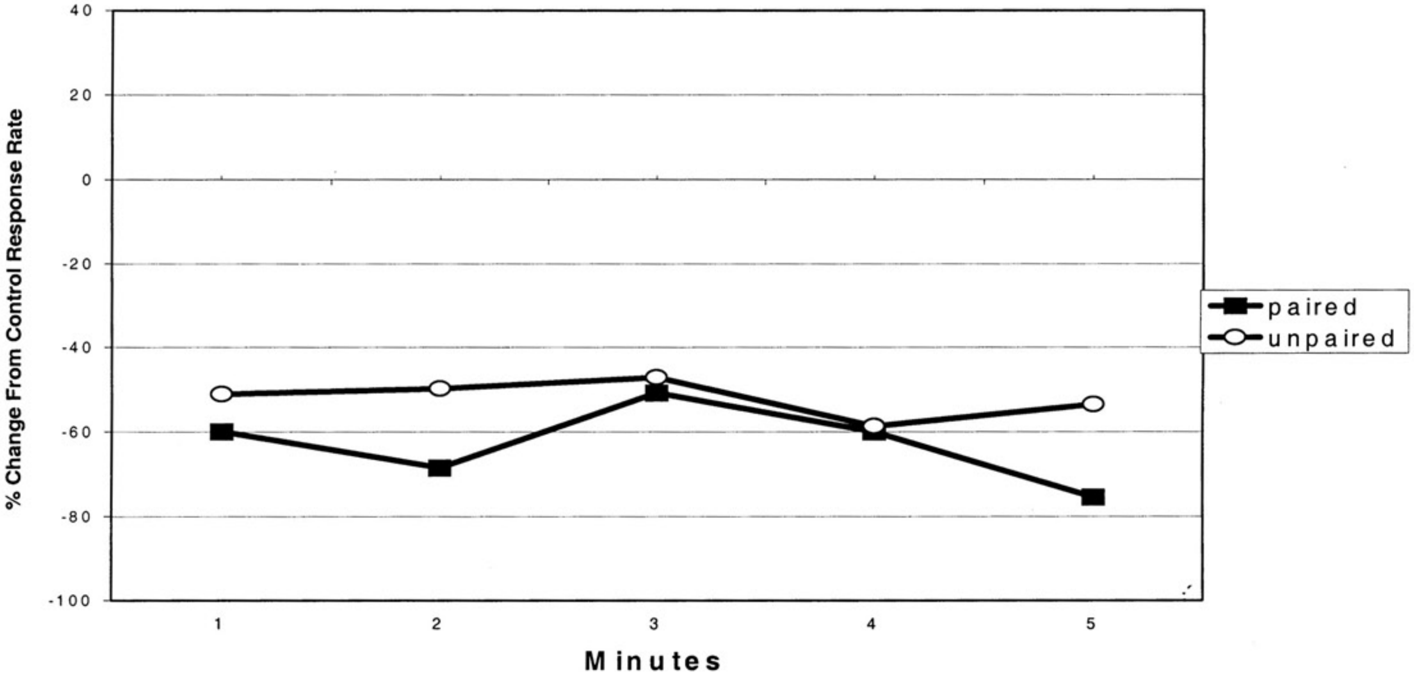


Figure 8: Yohimbine dose-response curve.

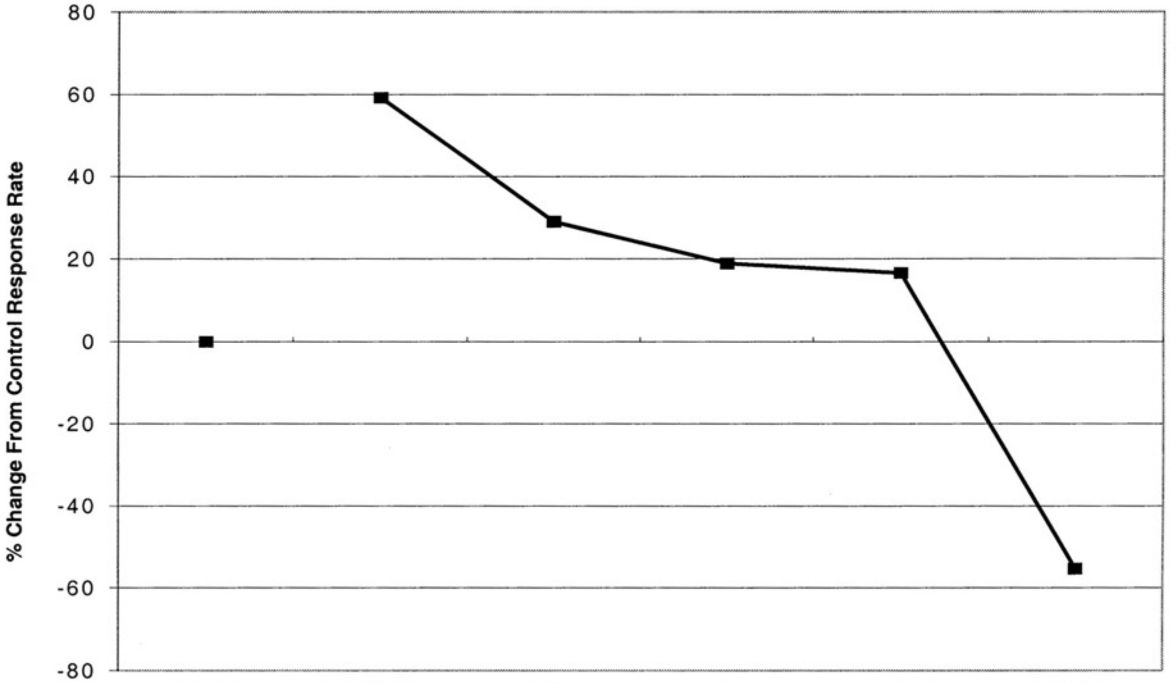


Figure 9: Mean group suppression across yohimbine doses.

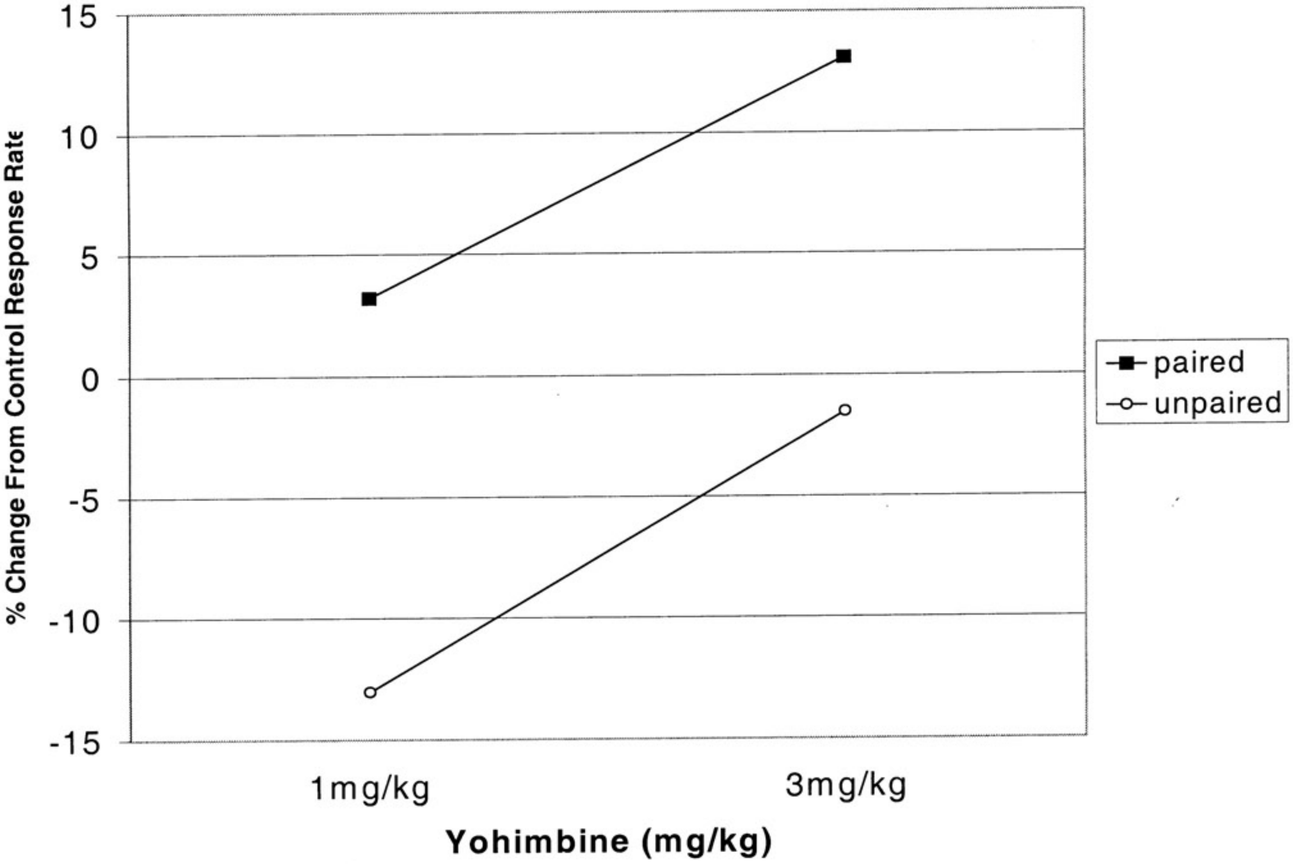
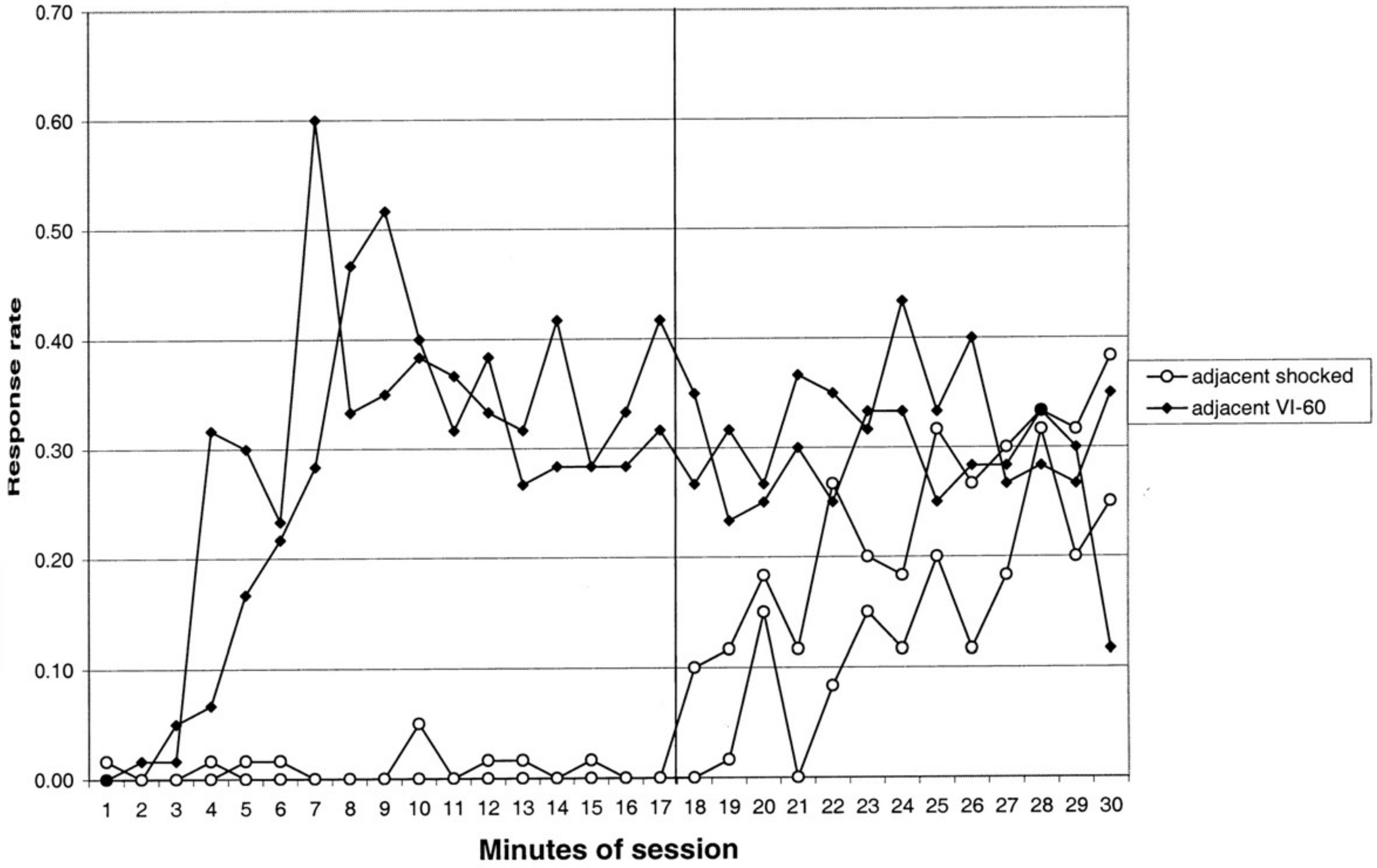


Figure 10: Rat #314 responding during four control sessions.



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